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## Original Articles.

### THE DIAGNOSIS AND MANAGEMENT OF VASOMOTOR DISTURBANCES OF THE UPPER AIR PASSAGES.\*

By J. L. GOODALE, M.D., BOSTON.

It has been known for some years that an individual sensitized to a given proteid may exhibit a characteristic reaction if the proteid is brought in a soluble form in sufficient concentration into contact with a scratch of the skin. In the present connection it is of importance for us to recognize and interpret correctly the significance of this skin reaction. I shall, therefore, briefly describe it and its various degrees of intensity.

The proteid to be tested is applied to a scratch on the skin of the arm. After five to fifteen minutes the positive reactions are indicated by varying degrees of local disturbance. These disturbances of the skin may be ranged in order of intensity as follows: In some cases the first perceptible alteration consists in a sharply circumscribed white area, not elevated, bordering the scratch for a distance of one to three millimeters. We may find in other individuals the first manifestation to consist of a slightly reddened raised area. In more pronounced disturbances the area of swelling is more extensive, and is more or less white in color, being surrounded by an area of reddening of

varying size. When this degree of disturbance appears, it is usually accompanied by itching. It may, in marked cases, attain a considerable size, the oedematous area reaching two to three centimeters or more in diameter and surrounded by a centimeter or more of hyperemia.

In the course of thirty minutes, or at most one hour, the reaction fades, and only the slight trauma occasioned by the scratch is left. In the case of certain proteids there may appear on the following day an alteration at the site of the scratch characterized by appearances of inflammation rather than of angioneurotic disturbance. The skin bordering the scratch becomes reddened, slightly elevated and firm. In the course of another twenty-four hours a trace of suppuration may supervene. These disturbances disappear in two or three days. It was at first thought that these inflammatory manifestations were the result of a chance infection, but they have occurred so regularly after testing with certain proteids as to suggest a definite relationship to the proteid substance itself. They follow most frequently tests with staphylococcus p. aureus and albus and streptococcus pyogenes. Among the foods, cocoa is apt to show it.

While the occurrence of the skin reaction may be regarded as indicative of sensitization to the proteid employed, yet it is premature to say that a direct relationship invariably exists. Certain observations, for instance, made in the course of hay-fever immunization, which I have elsewhere recorded, show that there is not always a skin reaction proportionate to the intensity of the nasal and ocular symptoms.

\* Read before the American Laryngological Association, May 9, 1916, at Washington, D. C.

During the past two years over four hundred cases showing vasomotor disturbances of the upper air passages were examined by the skin test with different proteids, for the purpose of determining, if possible, the diagnostic value of this reaction, and ascertaining its relationship to the clinical manifestations. For many of these disturbances the special exciting proteid was indicated by the patient's history, as in cases of hay-fever, intolerance to fish, horses, eggs, etc., but exclusive of the hay-fever patients, the larger number gave a clinical history in which the causative agent was unknown to the patient.

Cases of vasomotor rhinitis of recognizable reflex origin and asthma from cardiac and renal disease are not included. In many instances, particularly of nasal disturbances, the diagnosis of a reflex cause, such as from the genital organs, is difficult to establish, but wherever possible a physical examination from an internist or the family physician was obtained.

*Classification of Proteids.* Recent studies have established a phylogenetic classification of animals and plants, based upon the serum reactions. As the result of the studies, chiefly of Nuttall for animals and of Metz and Gohlke for plants, we are enabled to construct a phylogenetic tree for both kingdoms. The application of these studies to our subject is considerably simplified by our ability to eliminate many members of the animal and plant kingdoms, which have no direct relation to man.

*Animals.* The primitive proteid molecule in the animal kingdom represented by protozoa exhibits a differentiation in the direction of the molluscs or shell-fish, and passing upward gives off the branch of the crustacea. Above this are the vertebrates, with the branches respectively of fishes, birds, the main trunk terminating in the mammals. In the present connection the mammalian orders which concern us are represented by the domestic animals, and by those which serve as foods, or whose skins as articles of clothing.

*Plants.* The phylogenetic tree of the plant kingdom proceeds from the bacteria upward, and divides into the monocotyledons and dicotyledons, the first being represented chiefly by the large family of grasses and by the orders of iris and lily. The trunk of the dicotyledons terminates in the order Compositae, or family to which the ragweed belongs, and gives off along its course a large number of orders, which have been shown to be of anaphylactic significance, the most important members of these being the nuts, the legumes and the rose family.

*Preparation of Material.* It is of importance to have the test material in the form in which it exists when exciting symptoms. Consequently, we should have it either in the raw or cooked state, respectively, or in both, as the case may be.

It should also be in a stable form, and as pure and concentrated as possible.

This statement is especially emphasized by the fact that we find that different persons vary widely in their degree of sensitization to a given proteid; consequently, one person may react to a proteid dilution of a given strength, while another individual sensitized to the same proteid may require a hundred or more times greater strength of the solution to elicit an equivalent skin reaction.

In the case of animals, preparations should be made both of those parts capable of entering the respiratory mucous membrane, as flying scales or hairs, and also of the serum and of those parts ordinarily ingested, such as egg and milk. Extracts from the epidermal structures are easily obtained by placing scrapings from the skin, hairs or feathers respectively, in 12% alcohol. Sterilization is accomplished after a few days by the action of the alcohol, and the suspended particles of clear filtrate may then be used. The material may be tested for its sterility, but in no case have I found it contaminated, or even after months show signs of decomposition. These extracts appear to keep without deterioration, and I have now two made from horse epidermis, which have been kept at room temperature for over a year, and are apparently as active as when first prepared.

In the case of animal foods, crude but satisfactory material is readily prepared by expressing the juices in a meat press, and subjecting them to rapid desiccation by a blower.

The same method may be followed in the case of plant material. Oils may be removed by leaching with carbon tetrachloride. Both these animal and plant extracts may then be preserved when thoroughly dry without deterioration.

The proteids of egg and milk can be obtained commercially in the form of a pure powder as egg albumen and casein respectively.

While the refinement and separation of the different proteids present in a given material is desirable and represents a field of important research, yet the above-mentioned relatively crude preparations will suffice to answer our first clinical question as to whether the individual is sensitized to the material in question.

In the present work cases were examined both with preparations made along the above lines by Dr. Turnbull in the Throat Department of the Massachusetts General Hospital, and also by pure refined proteids prepared by Mr. R. P. Wodehouse in the Botanical Laboratories of Harvard University.

*Preparation of Bacteria.* Suspension of bacteria killed by coagulation of their albumen may be injected intradermally, and the presence or absence of a reaction noted on the following day, as already practised for a number of diagnostic tests, but I have also found it possible to procure the bacterial proteids in a soluble

form capable of exciting an immediate skin reaction in the same manner as that obtained from pollen and other plant and animal extracts. At the beginning of the work, cultures were grown by Dr. C. G. Page, instructor in bacteriology at the Harvard Medical School, on agar slants, when they were exposed to ether vapor, the object sought being to kill the microorganisms without coagulation of their albuminous constituents. After remaining in ether vapor four days, the colonies were transferred to a 12% dilution of alcohol with water, in order to extract, if possible, the proteids of the bacteria. This alcoholic dilution was chosen as it has been found by the writer to preserve best the anaphylactogenic properties of pollen and keratin extracts. The quantity of bacteria was about one-third by volume that of the alcohol dilution added; so that, on centrifuging, the bacterial bodies occupied one-third and the fluid two-thirds of the tubes. After a week, the fluids were tested on the skin of patients in the same manner as that employed for the diagnosis of plant sensitizations.

Since then a variety of methods of preparing bacteriological material has been developed by Dr. A. E. Steele of the Massachusetts General Hospital, Dr. I. C. Walker at the Peter Bent Brigham Hospital, Dr. Cleveland Floyd and Mr. H. M. Baker at the Harvard Medical School, to all of whom I am greatly indebted for the opportunity which they have given me to test preparations made with this object in view.

In the case of plant pollen, I prefer to keep it in a dry form, as it will then stay unchanged for an indefinite period. I have flowering specimens of grasses and of ragweed in my herbarium gathered over thirty years ago, the pollen of which still gives pronounced skin reactions in patients sensitized to these plants.

A method was evolved by Mr. Wodehouse for the extraction of ragweed pollen from the flower heads, which enables one to obtain it in a purer form than has hitherto been the case. Plants of ragweed are gathered in the flowering stage and the flowers stripped off. The habit of this plant is to open the flower heads in succession, and consequently at a given time some will be found to have discharged their pollen and others to be as yet unopened. After drying in air the heads of flowers were washed in carbon tetrachloride to remove oils, etc., and it was found that most of the pollen came out in the process. Very little solid matter except the pollen will pass through the muslin used for straining. The pollen grains having passed through are allowed to dry and are seen to be somewhat paler than those obtained in the natural way, the difference in color being probably due to the removal of lecithin.

The same method is applicable to the other anemophilous plants, which furnish a large amount of pollen.

We are thus enabled to obtain the pollen in a

relatively pure form and consequently can make solutions of known proteid strength. Furthermore, this material has not been subjected to the risk of change by treatment with proteid precipitants and approximates closely to the original proteids in their natural state, as they actually reach the exposed mucous membranes.

Experiments were undertaken in regard to preserving pollen and pollen extracts. As I have stated in a previous paper, a dilution of alcohol in water proved most serviceable. The important object to be attained is a solution which will check decomposition, with the minimum loss of strength of the active principle. It was found that pollen extract in 6% alcohol or less showed after a few days development of bacteria and proteid decomposition. A dilution of 8 to 10% was sufficient to check putrefaction, and if the bottle was completely filled with the solution it remained free from alteration. If, however, the bottle was frequently opened or left half full, there was a prompt invasion of the yeast organism with development of vinous odor. This was later followed by the appearance of the *Mycoderma vini* and general turbidity. Solutions from 12 to 15% could be left open without alteration and there was no development in them of the *Mycoderma*. These solutions were found to contain an unstable albumen and a relatively stable proteose. The former is readily coagulated by exposure to air, by treatment with alcohol of above 20%, and by heating to 60° C. The proteose, on the contrary, suffers but little on exposure to air, and will endure boiling without precipitation. This observation is in harmony with the familiar fact in wine-making that at the close of the first fermentation a clear fluid is present containing the albuminoids of the grape in solution. These are in part thrown down at the first racking and consequent exposure to oxygen, rendering the wine turbid, and requiring often the admixture of isinglass to effect a clarification.

For this reason pollen solutions should be kept as far as possible from exposure to air, and if in the older ones a cloudiness occurs, it should not be filtered, as thereby the albumen would be removed, leaving only the proteose in solution.

The globulins of the pollen grain were separated by Mr. Wodehouse, but were found to be without anaphylactogenic properties.

#### METHOD OF ENTRANCE OF FOREIGN PROTEIDS INTO THE BODY.

Obviously under natural conditions the mucous membranes of the respiratory and the intestinal tract afford ready means of access for these substances when inhaled or ingested, and we may consequently speak of such forms of allergy as (1) inhalation or (2) ingestion anaphylaxis.

The possible existence of a third form should be considered, namely where the symptoms may arise from (3) autolysis of bacterial proteids

when in contact with the mucous membranes. In a recent paper I have called attention to this possibility, and have shown that in certain cases of perennial vasomotor rhinitis and bronchitis, it is possible to elicit an immediate skin reaction by the application of soluble bacterial proteids to a scratch. Since this paper was written further observations have tended to confirm these views. Such cases are dependent upon the more or less periodic invasion of the mucous membranes by the bacteria to which the individual is sensitized; during the intervals of infection, the patient remaining free from vasomotor disturbance.

At least two other possible bacterial causes may exist. In the first instance it is theoretically possible that chronic septic foci, as in chronic tonsillitis, with accumulation of lacunar debris, may be the source of sensitizing proteids; also it is conceivable that the intestinal canal may permit the development of bacteria, which may undergo autolysis, and the consequent liberation of proteid material which is anaphylactic for the individual.

The above system of classification is a tentative one, and while for certain portions we may believe that we have sufficiently confirmatory evidence, we are not as yet in a position to accept it as a whole without further investigation.

In the present paper I have endeavored with this classification as a basis to study a series of vasomotor disturbances occurring in private practice and in the Throat Department of the Massachusetts General Hospital.

#### I. INHALATION ANAPHYLAXIS.

Under this heading two main types are recognizable, the first being seasonal, the second perennial. In the first instance we find that the symptoms appear at a definite time of the year, and are represented by the very large class of hay-fever patients, the symptoms coinciding with the flowering of the special plant in question. The second, or perennial form, occurs at any time of year whenever the exciting proteid enters the system through the respiratory tract, as in sneezing or asthma from the presence of horses and cats.

##### IA. SEASONAL INHALATION ANAPHYLAXIS OR HAY-FEVER.

In this affection recognition of the causative agent is considerably simplified by keeping in mind the following facts: In the first place our search should be chiefly directed to the monoecious or dioecious plants. As I have previously pointed out, it is those plants which distribute a large amount of pollen in the air which excite hay-fever symptoms. Entomophilous plants, which accomplish cross fertilization through the agency of insects, are able to be much more economical in the production of pollen, and it is

consequently not likely that such pollen can come in contact with exposed mucous surfaces under natural conditions. Such pollen, furthermore, is more viscid and sticky, the object evidently being to enable it to cling to the bodies of the insects which visit the plant in question. It is necessary, on the other hand, for anemophilous plants, which depend for their fertilization upon the agency of air currents, to produce a large amount of pollen, and pollen, furthermore, which is relatively light, and easily detached from the anthers.

Recognition of these facts enables us to determine with much more certainty the causes of hay-fever in a given locality. We may, therefore, pass over the entomophilous plants and confine our attention to the anemophilous representatives. Such are, in this vicinity, certain trees, especially maples and oaks, the grass family as a whole, and certain species of the wormwood family. Although the pines and other gymnosperms produce a very large amount of pollen, yet I have not so far found any instance of hay-fever being caused by them. It is in the next place necessary to consider the season of hay-fever symptoms. If they occur previous to the flowering of the grasses, we shall obviously have to look for the exciting cause in the early flowering shrubs and trees, and among these birch, maple and willow are chiefly responsible. About the middle or the last of May the oak begins to flower in this region, and tests should therefore be made for this family. The flowering period of these trees is relatively brief, and consequently the hay-fever occasioned by them is less likely to disturb seriously the patient's mode of life.

In the case of grasses we have a flowering period extending from the middle of May in this locality until the first week in July, and the attack of hay-fever which they may excite is not only more prolonged, but more severe.

Examination of the Compositae is very much simplified by recognizing that the proteid or active agent of all its members is essentially the same. While minor differences may exist, yet one active pollen will, for diagnostic purposes, cover the whole order. An interesting example of this is found in two of my patients who spend the winter in Cuba, and who there in February suffer severely from a plant known locally as *Escoba amarga*, used by the natives to keep fleas from their dwellings, which has been identified for me by Professor Oakes Ames as *Parthenium hysterophorus* Linn. After the return of these patients to Boston in the early spring, they are free from hay-fever until the flowering of the grasses, when a moderately severe amount of vasomotor irritation appears and lasts until the first of July. They then remain comfortable until the middle of August, when severe hay-fever appears and lasts until frost. Examination shows that these patients are sensitized to grasses and to ragweed, and that the Cuban

plant excites marked skin reaction. Tests of this plant on numerous other sufferers from ragweed, who have never been in Cuba, excite marked skin reaction in all cases.

Tests, furthermore, of different members of the Compositae, from the earliest flowering ones, such as coltsfoot, to the late blooming asters, show that with sufficiently strong solutions all ragweed cases will develop skin reactions. Under natural conditions, however, throughout the greater part of the United States, the chief exciting cause among the Compositae is found in the ragweed, the structure of which will repay examination. It will be seen that the plant is characterized by the possession of long spikes containing the male flowers, and by the localization of the female flowers at the base of the spikes. The amount of pollen which this plant distributes is very large, and it is also extremely light. The flowers open in succession, beginning with the central spike, a few discharging daily, and the scattering of the pollen being consequently maintained for a long period. Another plant of the Compositae which resembles the ragweed in its method of flowering is the *Baccharis halimifolia*, a favorite plant in shrubberies, although its power of causing hay-fever has not hitherto been recorded. The plants are dioecious, and the amount of pollen formed is considerable. The more showy members of the Compositae such as field daisy, golden rod, asters and other garden representatives, possess a relatively small amount of pollen, as well as one of a more generally viscid character. Patients consequently more readily escape, unless the plants are brought into the house.

Examination of the present series of cases has led to the conclusion that the number of proteid types concerned in exciting symptoms is much smaller, at least for New England, than has previously been supposed. During the period preceding the flowering of the grasses, nine cases presented symptoms which terminated by the first or the middle of May, according to the seasons. These patients showed no sensitization to grasses, but reacted chiefly to the maple, birch and willow. Fifty-seven cases showed sensitization to grasses, and 183 were positive to ragweed, and other members of the Compositae. Sensitization to members of the rose family alone was found in but one case, although a number were found in association with grass sensitization, where it was evident that grasses were the predominating factor.

With regard to the July or midseason forms of hay-fever, I believe that, with exception of the chestnut and possibly some garden flowers, the chief causes are found either in some special distribution or exposure to either late blooming grasses or early blooming Compositae.

It is at this season also that the cases of olfactory vasomotor rhinitis or pseudo-hay-fever are most commonly found. In this affection the

fragrance of certain heavily scented flowers excites vasomotor disturbances, ranging all the way from sneezing to acutal asthmatic paroxysms. The action of pollen can be definitely excluded by wetting or removing the anthers without influencing the vasomotor symptoms. Skin tests, furthermore, of the pollen show no reaction. The phenomena are plainly reflex, and the path of transmission appears to be along the olfactory rather than the optic nerve. The flowers most commonly responsible are lilies, hyacinths, sweet peas and peonies. The condition occurs either alone, or in association with true hay-fever, and is more common in neurotic or impressionable individuals, although not confined to such, several of my cases occurring in highly intelligent individuals, possessing no discoverable neurosis.

It may here be noted that during the hay-fever attack a general hypersensitiveness of the patient is apt to appear toward plants, for which at other seasons he shows only a minor or no reaction. One must therefore be on his guard at this time to observe carefully the relative preponderance or degree of development of the various skin reactions, and he will probably be safe in confining his therapeutic endeavors to the plant which causes the most marked disturbance.

#### IB. PERENNIAL INHALATION ANAPHYLAXIS.

(a) Of Plant Origin. Under this heading I have included those cases of vasomotor disturbance in which the exciting proteid is derived from some other part of the plant than the pollen. Two cases of severe sensitization to flour were found in bakers, who, however, had no hay-fever, and who did not react to wheat or grass pollen. These cases, furthermore, could eat bread without disturbance. One case of sensitization to potato was found in a cook. Eight cases of severe sneezing from orris root were encountered in women using face powder containing this as an ingredient. Both the crude root of *Iris Florentina* and the commercially prepared orris powder produced in these cases marked skin reactions and vasomotor disturbances. In several of these patients the cause of the symptoms had not been previously suspected, but in all instances a complete subsidence followed the discontinuance of the face powder.

(b) Of Animal Origin. Forty-nine cases were found of sensitization to epidermal scales and hairs of animals or feathers of birds. The symptoms varied from vasomotor rhinitis to severe asthma when inhaling fine suspended particles of the special exciting substance in question. In all cases a definite reaction was elicited by the application of a keratin extract to a scratch of the skin. While the majority were aware of their sensitization, yet for a number of individuals the first recognition of the

cause was obtained by the test. This was especially found in the case of children.

Of the various animals, the horse was represented by forty-two cases, the dog by eight, and the cat by six. The sheep and cow gave in two cases respectively moderate but apparently definite reaction to keratin extracts from the natural hair, but it did not appear that the first case was affected by the dust from woolen blankets. In two cases definite vasomotor rhinitis was occasioned by the use of feather pillows, and keratin extracts from feathers of the chicken or duck gave well-defined skin reactions. The symptoms disappeared on the discontinuance of the feather pillow.

A distinct difference appears to exist between the proteid of the serum and that of the epidermal structures in the animals studied. In the case of the horse eleven patients gave marked reactions to the keratin extract but no reaction to the serum either in pure powder or as antitoxine. That this difference is not due to greater strength of the keratin extract employed is shown both by the fact that the majority of patients gave equally marked reactions to both serum and keratin, and by the observation made in one individual of a pronounced cutaneous reaction to horse serum, without a trace of disturbance from the keratin. This patient had had but little to do with horses, but had, thirty-eight years previously, been bitten by a colt. It is conceivable that in this manner a sensitization to the serum alone may have developed.

While the majority of the dog and cat cases reacted to keratin, both clinically and by the tests, yet two individuals were discovered who reacted to dog serum in a marked degree without sensitization to dog hair. Two similar cases were found reacting to cat serum alone. These four individuals had no discomfort when in the neighborhood of dogs or cats respectively.

Of the two cases of feather sensitization, one showed no reaction to eggs.

These observations indicate the necessity of employing keratin extracts as well as sera, when making diagnostic tests of sensitization. Furthermore, the probability is suggested that certain cases of horse-fever or horse asthma may in reality receive antitoxine without anaphylactic shock, if their sensitization is to the hair and not to the serum of the animal. Finally, the possibility is conversely suggested that the absence of symptoms from horses does not preclude the possibility of an anaphylactic shock from the administration of antitoxine.

## II. INGESTION ANAPHYLAXIS.

Twenty-eight cases were characterized by a more or less well-defined sensitization to various foods. This number does not represent the true relative frequency of such cases, since their study has been undertaken only during the

past six months, and many of the earlier ones may have escaped recognition.

These cases represent all gradations ranging between sensitizations so slight as to have excited no subjective symptoms on the part of the patient and extreme susceptibility in which contact of the smallest part of the proteid in question caused profound general disturbance. It was noted that the local sensations were referred to the throat, rather than to the region of the stomach. Such symptoms were described variously as tickling or itching in the throat, or, in more severe cases, as swelling and smarting. The general constitutional phenomena were in some cases definite asthmatic symptoms, in others urticaria. Eczema was found associated in a number of instances; psoriasis occurred once.

Animal foods were prepared for testing, as already described, and instances were found of sensitization to shell-fish, crustacea, fish of various sorts, egg, milk and meat. If the skin reaction was marked, the patients were usually aware of their idiosyncrasy. This applies particularly to intolerance to fish and eggs.

Milk was found in one instance to give severe asthma in a child seven years of age. This patient had had more or less constant asthma since being weaned. Physical examination by Dr. J. L. Morse was negative. The skin tests showed reaction to milk, horse and cat keratin. On discontinuing the milk, and keeping the cat away, the asthma ceased completely. At the end of two weeks the child was given cow's milk again, with a return of the asthmatic symptoms. This was allowed to continue for a week, and the milk discontinued, the asthma simultaneously disappearing. A week later he was allowed to play with the cat, whereupon asthma reappeared. On keeping him away from the cat, and giving milk at the beginning in drop doses, and gradually increasing, it was possible at the end of six months to establish a tolerance for a glass of milk. The child has during this time been free from asthma.

Cases of sensitization to egg have been referred to children's specialists for immunization by progressive doses, with successful results.

A case of sensitization to raw animal sera was found in a boy twelve years of age. This individual reacted to dog, cat, hog, sheep and ox serum, to a high degree. Horse serum and goat serum excited slight reaction. Guinea-pig serum gave no reaction. Tests with cooked beef and lamb gave no reaction. There was well-defined sensitization to keratin of dog, cat, horse and lamb, but none to that of the ox. Commercial casein and egg gave no reaction. This case indicates the desirability of having the animal foods prepared for testing under the form in which they are usually taken into the system.

In the case of plant foods we have likewise to prepare the material in the raw, boiled or roasted state, as the case may be. A variety of

proteid substances exists in plants, the greater part of which is coagulable by heat. While many proteid substances in aqueous solution require a temperature of 100° C. before being coagulated, others coagulate at 65° C. Proteoses withstand boiling, but may be precipitated by treatment with absolute alcohol. Eleven cases were found of sensitization to grains. In certain of these the patients had no subjective sensations. In four, however, it seemed probable that the asthmatic symptoms of which they complained were attributable to the eating of grains in the form of cereals and bread. Two of these cases are reported somewhat in detail.

CASE 1. G., 40. Asthma, since childhood, of unknown origin, more or less persistent throughout the year. No reactions were found to animal foods or to the pollen of grasses, and the patient had no hay-fever. Raw and boiled proteids of wheat, barley, oat, corn and rice gave marked skin reactions. Proteids extracted from the inside of bread gave reactions much less pronounced than the raw or the boiled material. Extracts prepared from well-browned toast and some roasted grains of wheat, corn and rice gave no reaction whatever. Various breakfast foods were tested, shredded wheat, triscuit, corn flakes, force, Kellogg's wheat biscuit and puffed rice giving no skin reaction. Grapenuts gave a pronounced reaction. The patient was negative for other plant foods with the exception of beans and peas. Bread and boiled cereals were omitted from his diet for a period of two weeks, during which time his asthma became much less, giving him at the close of this time practically no discomfort except on exertion. On eating again freely of bread, after two days the asthma returned in its original intensity, diminishing later when bread was omitted. When the roasted cereal foods above mentioned, which gave negative reactions, were introduced into the diet, there was no return of the asthmatic symptoms, and the patient is now in greatly improved general health.

CASE 2. S., 35. Asthma many years more or less constant. Hay-fever in spring, moderate. Marked reaction to wheat, raw and boiled, and to bread proteid. Marked reactions to raw and boiled proteids of oat, barley, rice and corn. Positive reactions were obtained also for cocoa and buckwheat. Squash, pea, almond, and Brazil-nut gave pronounced reactions. There was no reaction to beet, turnip, cabbage, parsnip, potato, eggs, fish or meat. This case was relieved very much of his asthma on omitting bread and grains, and the other plant foods to which he was sensitized. A proteid extract of wheat was treated with pancreatin for three days. This modified extract caused marked skin reactions. Wheat, rice and corn, heated to a temperature of 115° C., gave no reaction, and their proteids on treatment with pancreatin for three days gave no reaction.

These two cases indicate that certain proteids present in the grains are heat stable up to 100° C., but at 115° C. their anaphylactogenic property is destroyed, and is not reintroduced by pancreatic digestion.

Four cases of sensitization to potato, both raw

and boiled, were observed. In one of these only was there any systemic disturbance, this consisting in an urticarial eruption. Proteids from baked potatoes gave no skin reaction.

Cases were also encountered of sensitization to nuts, both walnuts, chestnuts, and Brazil nuts, some reacting also to almond, although this is derived from the rose family, and stands far removed in a botanical classification from the others. These cases did not react to the pollen of chestnut or the rose family, respectively. A few cases were found of sensitization to strawberries, bananas, oranges and apples in the raw state. Cooking, however, of the strawberries and apples made it possible for the patients to eat the fruits without discomfort. The inference here to be drawn is that the sensitizing proteid was coagulated or destroyed on boiling. The cases of clinical sensitization to grains as a rule had no hay-fever, and did not react to the pollen of grasses. It was, however, observed that cases of marked sensitization to grass pollen gave without exception a definite skin reaction to proteids, both boiled and raw, of grains. This observation suggests the probability that the pollen represents the specific plant proteid found throughout all its parts, as Metz and Gohlke have apparently shown, but that in the development of the ovule during the summer other proteids are formed with anaphylactogenic properties differing from those of the specific plant proteid, and that these seed and fruit proteids represent a high degree of differentiation among closely related species. This clinical observation receives confirmation from the works of Wells and Osborne.

These observers have isolated from the seeds of closely allied plants substances resembling proteoses, which are distinguishable from each other. They reach the conclusion that resemblances and differences of these substances are dependent upon the chemical constitution of the proteid molecule, rather than upon biological differences. They, for instance, found that zein, the alcohol soluble protein of corn, did not cause the anaphylactic reaction in animals sensitized with gliadin, the alcohol soluble proteid of wheat, nor with hordein, the alcohol soluble protein of barley. At that time hordein and gliadin had not been tested against one another, but it had been observed that preparations of gliadin from either wheat or rye interacted against one another, as if they were one and the same protein. On testing hordein from barley against gliadin from either wheat or rye, they have since found that these two proteins of different origin also react with one another. Furthermore, they have found, that while preparations of gliadin from wheat reacted anaphylactically with glutenin from the same seed, hordein from barley fails to cause reactions in guinea-pigs sensitized with glutenin.

It has seemed to me possible that these relationships between the specific plant proteid

found in the pollen, and those of the seeds and fruits may be represented graphically as follows: Taking, for instance, the Rosaceae, we may let A represent the specific proteid of the family found in the pollen and throughout all the parts of the plant. B, C and D may be taken to denote the fruit proteids of the apple, strawberry and almond, elaborated by the activity of the respective plants during the summer's growth. The proteids present in the fruits will therefore be AB, AC and AD. An individual sensitized to the pollen of the rose will react positively to the pollen of all the members of that order, and will also react to extracts from the fruits or seeds of all. If, however, he is sensitized to proteid B of the apple, he will react neither to the pollen of any of the rose family nor to proteid C of the strawberry nor to proteid D of the almond.

This hypothesis has apparently received confirmation from my observations on the Rosaceae and Gramineae, as already mentioned.

### III. AUTOLYSIS OF BACTERIAL PROTEIDS.

While the influence of proteids from animals and from flowering plants in the causation of anaphylactic symptoms is sufficiently recognized, yet the part which possibly bacterial proteids may play in these conditions is not yet clear. Clinically we find a large number of cases in which the influence of bacteria seems probable. We may divide these conditions provisionally into acute recurrent and chronic forms. In the first instance we find that the individual goes for considerable periods of time with little or no vasomotor disturbance, and that with the advent of an acute infection of the nasal or bronchial mucous membrane, he exhibits symptoms of vasomotor rhinitis or of asthma. The mucous membranes in these conditions do not show reddening or pus formation which are characteristic of acute rhinitis and acute bronchitis, but present rather the typical picture of hay-fever. After the cessation of the acute symptoms, the individual is free from asthma until the occurrence of another infection. The existence of chronic forms of bacterial infection have been recognized by clinicians as being represented on the one hand by chronic sinusitis and on the other by intestinal stasis, and we have probably all had cases where treatment or cure of these conditions has resulted in relieving the vasomotor symptoms. I believe that chronic lacunar tonsillitis with accumulation of detritus must be regarded also as a possible cause of proteid absorption.

In a recent paper<sup>6</sup> I have called attention to the possible explanation of such types of vasomotor disturbance, referring them to the solution or autolysis of bacterial proteids, to which the patient is sensitized. On this hypothesis both these acute and chronic forms of vasomotor rhinitis and asthma are dependent upon the occasional or constant anaphylactogenic action of

autolyzed bacteria. Experiments which were then reported for the purpose of determining whether bacterial proteids in solution could elicit skin reaction, showed that out of fifty cases positive reactions were obtained from the staphylococcus p. albus, aureus and citreus; also from a bacillus of the Friedlander type, and the micrococcus tetragenus. Since then further study has confirmed these observations, and reactions have been obtained in a number of cases from the bacillus of influenza, streptococcus pyogenes and viridans and the pneumococcus, Types I and II. It was also observed that after an attack of asthma the skin reaction could not be elicited, but returned again after a few weeks. Much still remains to be done before conclusions can be drawn as to the relation of these organisms to the vasomotor disturbance in question. If it should be confirmed that definite sensitizations to microorganisms exist on the part of these anaphylactic cases, our therapeutic work should receive a highly important assistance. We should, for instance, in the case of acute recurrent infections, be guided in the choice and administration of vaccines. The cases of chronic proteid absorption would be more intelligently approached in that we should be led to examine the patient with especial care for the purpose of removing, if possible, the foci of infection, or at least of draining and cleansing the regions in which prolonged contact of bacterial proteids may occur.

### ASSOCIATION OF FACTORS AND THE OCCURRENCE OF CLINICAL SYMPTOMS.

A review of the cases has shown that for the majority a variety of sensitizations is present. We find, for instance, often hay-fever disturbances from the pollen of different orders, while here and there hay-fever patients occur with sensitization also to bacterial proteids, certain classes of foods, or keratin desquamations.

In such cases our task is first to determine the factor which is responsible for the symptoms, and to place in proper perspective the relative influence of the other sensitizations to which the patient is subject. The line of inquiry is usually as follows: First, Are the symptoms strictly seasonal? In this case we shall obviously be able to disregard all factors except the various pollens. If the symptoms are perennial, inquiry is next made as to their relation to the occurrence of colds and acute infections. If the answer is confirmative and the patient states he is entirely free from discomfort except when suffering from a cold or acute bronchitis, we may feel justified in disregarding the influence of both inhaled and ingested proteids, and devote our attention to an examination of his reactions to the various bacteria concerned in acute infections of the upper air passages.

If the symptoms are more or less constant throughout the year, the possible influence of

domestic animals should be sought for, especially dogs and cats in the case of children. Nor must the possibility of orris root in toilet or sachet powder be forgotten. Inquiry is next made as to disturbance from different articles of foods, and here the tests should be first made for such substances as enter habitually into the diet. Thus, in order of importance, we place eggs, milk, meat, grains, legumes and potatoes, since if the patient is not sensitized to any of these, it is unlikely that the more occasional articles of diet, such as shell-fish, fish, root vegetables, greens and fruits are responsible.

If the above tests have resulted negatively, our attention should be directed to the possible existence of chronic absorption of bacterial proteids, and we may then proceed with the examination of the patient, as to his sinuses, tonsils and gastro-intestinal tract.

#### THE MANAGEMENT OF PATIENTS SHOWING HYPER-SUSCEPTIBILITY.

In symptoms arising from inhalation of sensitizing substances, if the exposure is likely to continue throughout the year, it is probably wiser to avoid the irritation than to seek to immunize the patient against it. We have at least as yet no record of successful immunization. A case which I reported last year of attempted immunization against horse asthma by the injection of horse serum and keratin extract showed a gain in tolerance to the presence of horses, but on the discontinuation of the treatment, the immunity was gradually lost, and the patient has now regained her original sensitiveness. Since for the successful preservation of the acquired resistance continuation of proteid administration is necessary, and inasmuch as we have yet developed no successful method which the patients would be willing to carry out for an indefinite period, it would seem preferable for the patient to accept his disability, and make the best of it.

Immunization against hay-fever by the injection of plant proteids has been described by other writers, and by myself in a previous paper, so that I shall not consider it here in detail. Before, however, we undertake the treatment, we should first decide whether the patient's discomfort is sufficient to justify us in starting him upon a course of procedure which may prove time-consuming and not wholly devoid of risk. The treatment is by no means to be compared to typhoid inoculation, but will require numerous visits with careful tests of the degree of progress in order to determine the correct dose for each occasion. I cannot too strongly emphasize the importance of this matter of dosage. We are dealing with agents capable in moderate overdose of causing unpleasant shock, and in sufficient amount, of leading promptly to a fatal result. The best advice that I can give one starting in this work is to test continually the patient's resistance, and to increase

the doses gradually in conformity with the skin or conjunctival tests.

In reviewing the results thus far obtained in three years' treatment of hay-fever by hypodermic injection, one must in the first place be guarded in accepting the statements of the patients themselves. As I have previously pointed out, seasons vary, and the physical condition of the patient may, likewise, differ from year to year. Patients are all too ready to attribute a greater freedom from hay-fever symptoms to the treatment employed. It is only where the patient's statements are controlled by clinical tests that they may be accepted as possessing value. With this preliminary statement I will say that the majority of patients who received treatment in the past two summers expressed themselves as satisfied with the results accomplished. From those who felt themselves improved, however, a considerable number should be eliminated, as careful examination of their surroundings, the season and their physical condition might permit other explanations of the diminution in symptoms. The typical individual who presented himself for treatment two or three months before the expected season showed a progressive diminution in the intensity of the skin reactions, and a greater tolerance to the solution employed. In most, instances, however, the patients did not escape entirely the hay-fever symptoms when the season came around. The typical behavior was as follows: Hay-fever appeared at the usual time or somewhat later, the latter possibly attributable to the season, and reached within a few days nearly its accustomed degree of intensity. This was, however, followed by a striking diminution in the symptoms, so that after the acme of discomfort had been reached, a very considerable degree of relief supervened, and most of these cases remained relatively or entirely free from trouble through the balance of the season. The impression was given in such cases that the amount of treatment which it had been possible to administer in the few weeks before the season was insufficient to effect a complete immunity, but that with the arrival of the season enough pollen was absorbed through the mucous membrane to push the patient, so to speak, over the line. The same results were apparently obtained when treatment was instituted at the beginning of the hay-fever season, and in the majority of such instances it was possible to bring about a relief of hay-fever symptoms several weeks before relief would ordinarily have been due.

I have received the impression consequently that we are not likely in the majority of cases with the present methods to do away completely with hay-fever symptoms in the course of a single season, but that, nevertheless, sufficient relief may be obtained to make it worth while to continue this method.

Where, however, treatment has been carried on during one season with more or less success,

it has been evident that a second course of treatment the following season is more distinctly efficacious.

The usual course of events here is as follows:

At the close of the first hay-fever season one finds that the patient has attained a relatively high degree of immunity, which in the course of the winter progressively diminishes. Beginning again next season several weeks before the expected date for hay-fever, one injects a small dose carefully determined in the usual way, and follows this by larger doses. In practically all such cases a rapid striking diminution in the intensity of the skin reaction was observed, much more speedy than was the case during the first season. Such cases when the hay-fever season arrived were distinctly more benefited than during the previous year, more than half showing no or exceedingly trifling symptoms. The work is yet too young to enable us to say with certainty what the future will bring forth, but with our present information I should advise considerable caution in the statements to be made to the patients, and especially to explain to them that they may observe little or no benefit during the first season, but that the results obtained lead us to advise a following out of treatment for two years, with the reasonable expectation that the second season's treatment will be more helpful than the first.

Although feeding experiments in the past with extracts of ragweed do not appear to have been sufficiently successful to justify their general adoption, yet the work which internists have done with the treatment of egg sensitizations, has suggested the possibility that we may accomplish similar results by administering foods in a natural state derived from the order which produced the symptoms. Experiments were consequently undertaken during the past summer to determine whether the patients sensitized to ragweed pollen would present symptoms from the ingestion of proteid foods derived from the same family.

It was thought that if such internal administration was followed by the development of vasomotor symptoms, either of the skin or of the mucous membranes, an immunization might possibly be accomplished along the recognized lines of treating egg and other food sensitizations.

For this purpose sunflower and lettuce were taken, both being plants of the Compositae, to which the ragweed also belongs. The pollen of both was found to excite marked skin reaction in cases of autumnal hay-fever.

Extracts were made from the seeds of the Russian sunflower which gave positive results, but the intensity of the skin reaction was inferior to that excited by the pollen. The seeds were given to ten hay-fever patients with the direction that they should chew them thoroughly and swallow shortly before their regular meals, with the idea that a certain amount of

the proteid might pass into the system directly without digestive alteration. In nine adult cases, however, no gastric discomfort was noted or any influence upon the hay-fever symptoms. Oil-free meal from sunflower seeds was prepared, which on the skin excited a moderate or marked skin reaction, depending upon the sensitization of the individual. This was administered internally in doses of one to two grams, without exciting symptoms of any kind whatever. One patient, a boy, said that his hay-fever was made worse after eating the sunflower seeds.

In the case of lettuce a strong extract was made from the seeds in a 5% sodium chloride solution, which gave a weak reaction. A strong solution of lettuce leaves in a 10% sodium chloride solution (proteins shown to be present by preliminary test) gave a negative reaction.

The amount of proteid present in the lettuce leaf is evidently too small to excite any disturbance, and with one doubtful exception, no patients had noted any influence upon their hay-fever from eating it in abundance.

It would appear consequently probable that we have no foods of the Compositae order, the ingestion of which is likely to influence the course of ragweed hay-fever.

In the course of this work it has become evident that many individuals exist who show definite anaphylactic skin reactions to various classes of foods, and the problem which here confronts us is to determine to what extent the clinical vasomotor symptoms are dependent upon such a hypersusceptibility. It has in some instances seemed indicated that certain individuals possess food sensitizations either partly developed or measurably overcome through the acquisition of progressively increasing tolerance, in whom the actual vasomotor explosion is in reality dependent upon some other proteid cause. The following case illustrates this possibility.

D., male, 40. Asthma severe, nearly constant for many years. Marked polypoid degeneration of middle turbinates with involvement of antra. Skin tests were positive for staphylococcus p. albus and a diphtheroid bacillus; negative for pneumococcus, the influenza bacillus, micrococcus catarrhalis and staphylococcus p. aureus. Positive reactions were obtained from proteid extracts of wheat, barley, corn, rice, pea, orange and cocoa. Negative or slight reactions were obtained from egg, milk, beef, mutton, fish, potato, carrot, beet, parsnip, squash and cabbage. Keratin extracts of domestic animals and birds were negative. The patient was put upon a diet containing only those foods to which he was negative, but without perceptible influence upon the asthma. No operation has as yet been done upon his sinuses, but in view of the above observations this seems the measure most reasonable to undertake.

Conditions of highly developed sensitization to foods have been studied by numerous observ-

ers, especially Schloss, Talbot and Chappell. It has been evident that children are much more prone to exhibit anaphylactic phenomena from foods than is the case in adults,—a fact possibly due to the greater absorptive power of the gastric mucous membrane in children, or to the acquisition of partial immunity in adults.

If the proteid enters into the accepted articles of diet, experiments have shown that immunity can be obtained in the majority of cases by administering it in small and progressively increasing amount. The details of treatment may be found sufficiently described by the authors mentioned.

The management of cases in which the vasomotor symptoms either demonstrably or by exclusion are attributable to the absorption through the mucous membrane of bacterial proteids is to be undertaken along lines already indicated. Acute recurrent infections may perhaps be checked by the administration of vaccines. The sensitized individual presents here an advantage in that it may be found possible to select for him with accuracy the special organism required.

Foci of chronic inflammation or sepsis should be drained or removed. In three of my cases of long-standing asthma, the excision of septic tonsils was followed by entire relief.

Cases of intestinal stasis should be treated by the internist or the orthopedic surgeon, as circumstances may require. Two cases of asthma with ptosis of the viscera were relieved by the application of a proper support.

#### CONCLUSIONS.

In a large proportion of vasomotor diseases of the upper air passages the disturbances are dependent upon the entrance of a foreign proteid into the system. The method of entrance may be through the contact of the proteid in question with mucous membranes of the respiratory or of the gastro-intestinal tract by inhalation or ingestion respectively. Foreign proteids may perhaps also develop in or upon these mucous membranes through autolysis of pathogenic or saprophytic bacteria. The application of the skin test to these conditions is of diagnostic value when employed with a recognition of the phylogenetic relationships of animals and plants, as determined by studies in serobiology.

Proteid material for testing should be prepared both from the keratin and sera of domestic animals, from the pollen of the chief causes of hay-fever, and from the various articles of food, which enter commonly into the diet. Bacterial proteids derived from the various invaders of the respiratory tract should be available either in solution or in soluble form.

When the skin reactions to the various classes of pollen proteids have been determined, the management of cases will depend largely upon the relative preponderance of the local reactions

in relation to the clinical history. If the cause is found to be seasonal, as in hay-fever, immunizing treatment by injection of pollen extracts is likely to prove of service. The sensitization returns during the following winter, and treatment must probably be repeated annually. If the cause is perennial and is due to inhalation of foreign proteids, it is wiser to avoid the cause rather than to seek to effect a cure by immunization. If the disturbing proteid enters into the ordinary articles of diet, a tolerance may be gradually established by feeding the substance in progressively increasing doses. Disturbances of bacterial origin have not yet been sufficiently studied to enable the formulation of a definite plan of treatment; but the results of these investigations confirm our present methods of treatment, and emphasize the importance of draining regions which can retain the products of bacterial activity. Septic foci should be removed. Vaccine therapy is likely in such anaphylactic cases to be more accurately guided than in the ordinary individual.

The results already accomplished in the case of this clinical investigation has led me to the conclusion that we possess in the intelligent application of the skin test a very definite aid in the diagnosis and consequent management of our cases of vasomotor disturbances of the upper air passages. We are as yet only at the entrance of this field, and its exploration must be carried out by the coöperation of laboratory workers in chemistry and serobiology.

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## ASTHMA IN CHILDREN, II. ITS RELATION TO ANAPHYLAXIS.

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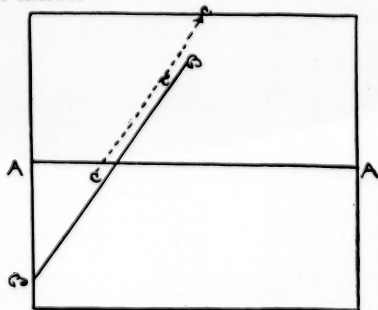
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In 1914 the writer reported six cases of asthma in children due to eggs.<sup>1</sup> Later, more careful review of the literature showed that Meltzer<sup>2</sup> was one of the earliest investigators to attribute the symptoms of asthma to anaphylaxis, on the basis of observations he had made on animals. Koessler<sup>3</sup> (1913) and Lesné and Richet<sup>4</sup> (1913) reported cases of asthma in young children caused by eggs. Richet<sup>5</sup> noted that cooking diminishes, but does not always remove, the toxicity of eggs. Recently opportunity has been afforded to study a series of cases

which have modified and broadened the conception of the etiological factors concerned in the production of asthma, and much more delicate materials have been used in the tests.

The histories of most of the cases studied have shown that there is a hereditary predisposition to allergy; that the parents or close relatives of the children have asthma, hay fever, or an idiosyncrasy to some food. During the year of 1914-15 the writer made a routine skin test for egg albumen on all the children and infants admitted to the Children's Ward at the Massachusetts General Hospital, and out of 85 admissions, three infants gave a positive skin test to egg albumen. They were respectively, three, four and eight months of age. The mothers of the infants, on being carefully questioned, said that the babies had never eaten egg in any form. A fourth case, in private practice, aged fourteen months, which had never eaten egg, gave a positive skin test to egg white. Schloss and Worthen<sup>6</sup> report the same results in two infants, and Blackfan<sup>7</sup> in one nine weeks old infant. It seems certain, therefore, that these infants had a hereditary and not an acquired sensitization to egg.

Sensitization may be acquired. It has been shown that the intestinal mucous membrane of the new-born infant is permeable to foreign protein for a short time after birth, and that later the foreign protein will not pass through the mucous membrane into the blood (when given in normal amounts), unless the mucous membrane is damaged.<sup>8</sup> Recently Schloss and Worthen<sup>6</sup> showed that whereas the healthy digestive canal of infants could take care of a small amount of foreign albumen (in this instance, egg albumen), large amounts passed through the intestinal mucous membrane unchanged, and could be demonstrated in both the blood and the urine. This investigation is of great importance since it explains many phases of asthma for which no satisfactory explanation could be given. Graphically it may be shown as follows:



A-A The limit of tolerance to foreign protein.  
B-B Increasing amounts of foreign protein.  
C-C To infinity.

Diagram of theoretical action of foreign protein in a sensitive case.

Any amount of the foreign protein below the line A-A, which represents the limit of tolerance, will be digested and changed so that none enters the body, while any greater amount will gain entrance to the body through the intestinal mucous membrane. Let the line B-B represent increasing amounts of foreign protein (for example, egg albumen). When the line B-B passes above the line A-A, the amount of protein given is greater than can be tolerated, and presumably passes into the body unchanged. One of two things results,—either the limit of tolerance is increased and immunity is established for that amount, as shown by diverting line A up the dotted line C-C, or some symptoms appear, which make it impossible to continue with such large amounts of the foreign protein.

During the past two and a half years a series of investigations, especially by Goodale<sup>9</sup> and Walker,<sup>10</sup> have made it possible to divide asthma and the allied condition, hay fever, etiologically into three types.\*

|                         |   |
|-------------------------|---|
| Inspired                | Hay fever—pollens <sup>9</sup>                            |
|                         | Dust and hairs from animals <sup>10</sup> , <sup>11</sup> |
|                         | Horse<br>Cat<br>Dog<br>Guinea-pig, etc.                   |
|                         | (a) animal foods, egg, beef juice, etc.                   |
|                         | (b) vegetables, oatmeal, lentils, etc.                    |
| Ingested foods          | (c) milk  |
|                         | (d) fruits  |
|                         | (e) nuts  |
|                         | (f) fish and shell fish                                   |
| Bacterial <sup>12</sup> |   |

The problem in children is quite different from that in adults, since during the first year of life sensitization to the foods alone is seen. The youngest recorded cases of asthma are respectively fourteen and twenty-eight days old.<sup>13</sup> As the child grows older, inspired asthma becomes more frequent, with increasing exposure to pollens and dusts, but this type is only a small proportion of the whole. A larger proportion of cases are still due to foods, and for that reason the writer's investigations have been confined almost wholly to the foodstuffs.

Since food idiosyncrasies and allergy, with resulting asthma, tend to cure themselves spontaneously in childhood, the proportion of cases of asthma due to ingested foods becomes smaller with increasing age, while the proportion of those due to inspired materials become larger. In later childhood and adult life there were many puzzling cases which were unexplainable until Goodale showed that asthmatics may give a positive skin test to bacteria, which presumably explains this group of cases. As the child becomes older it contracts infectious diseases, which, on proper soil, may be so spaced in time as to cause the patient to become allergic. The bacterial type of asthma is relatively rare in

\* The writer reiterates here what he said in the first paper on Asthma in Children, viz., that only those cases are asthma in which renal, cardiac, thymic asthma, and asthma due to enlargement of the bronchial glands have been excluded.

childhood (the writer's tests so far have all been negative), and more common in the adult.

There is yet another group of cases which give negative skin tests, and in which no etiological cause for the asthma can be found. The explanation may be that either the materials used in the tests were not concentrated or strong enough, or the proper materials were not selected, or that there is still another type of asthma.

The writer has followed forty-five cases of asthma in childhood over a period of several years. Five of these cases gave a history of egg idiosyncrasy, but have outgrown the idiosyncrasy and asthma without treatment, and are thus consistent with the general opinion in text-books, that children are apt to outgrow asthma.

During the course of the past three years the methods of determining the etiological cause of asthma have improved both in the technique and in the materials used in the tests. The skin test is performed as follows: A linear scarification is made about one-half an inch long, and only deep enough to penetrate the outer layers of the skin, care being taken not to draw the blood. In each case an extra scarification is made as a control, because it is a well-established fact that the mechanical injury to the skin may result in a pseudo-reaction (an elevated white area surrounded by a small roseola), especially in patients with an "exudative diathesis."<sup>14</sup> The scarifications are then inoculated by placing the materials to be tested (preferably in fresh solution) on the scarifications, and watching them for twenty minutes. A positive reaction appears in from two to ten minutes, and in rare instances a delayed reaction is seen in one to two hours. A positive reaction gives an urticarial wheal with an irregular outline surrounded by a pink blush, both of these phenomena being absent in the control. In some cases the blush, without the urticarial wheal, is so pronounced that there is no question that there is a positive reaction. Itching may or may not be present. The reaction usually disappears within one-half to two hours. The more delicate the skin the more sensitive it is to a foreign protein, and the more readily will it react even when it is unbroken or only slightly broken. The skin of an infant reacts very readily, and even when healthy is capable of absorbing the foreign protein in some instances. When the skin becomes thicker and hardened by exposure, as in the male adult, it reacts less readily, requires a more concentrated test solution, and a deeper scarification. Children and young women with delicate skins react almost as easily as do infants. The skin of the inner

flexor surface of the arm is thinner and more sensitive than that of the outer arm, and for that reason is the best place to make the scarifications.

The materials used in the skin tests were at first watery extracts of cereals, and expressed juices (whenever they could be obtained), and were prepared freshly in the office. Later the pure proteins of various vegetables, fruits, and nuts were prepared by Mr. Wodehouse working in the Botanic Garden at Harvard College, and found to be more satisfactory than the home-made product. They contain a more concentrated solution and do not deteriorate. Naturally, the scope of this investigation increased with the number of materials which could be tested, and the thoroughness with which the cases were studied increased with the materials prepared for the tests.

Of the 45 cases in this series there were thirteen in which the skin tests gave no clue to the etiological cause of the asthma. They were either not tested with the proper material or they were anti-anaphylactic.<sup>15</sup> The difficulty of finding the cause of the asthma is shown by a case in which 38 tests were made before positive information was obtained.

Twenty-three cases of the series have been carefully studied, and of these 18 had eczema at some time or other. This is a higher proportion than that reported by Berkhard,<sup>16</sup> who found that in 117 cases, 44 had eczema simultaneously. A family history of asthma, hay fever, rose colds, eczema, or idiosyncrasy to some food was present in 19 out of the 23 cases, while in the remaining four cases there were no notes, in the family history, on these points. Berkhard also found a "hereditary element" strongly marked in 16% of his cases. It seems, therefore, that there is a strong family predisposition to asthma.

In 19 of the 23 cases selected from this series there was a positive skin test to fresh egg albumen.

Out of the total 45 cases the following positive skin tests were obtained:

|                                      |    |
|--------------------------------------|----|
| Eggs .....                           | 27 |
| Beef juice.....                      | 5  |
| Rice flour (crude) (a).....          | 2  |
| Oatmeal flour (crude) (a).....       | 2  |
| Green pea (crude) (a).....           | 1  |
| Kidney bean (crude) (a).....         | 1  |
| Lima bean (crude) (a).....           | 1  |
| Black bean (crude) (a).....          | 1  |
| California pea bean (crude) (a)..... | 1  |
| Dry cow casein.....                  | 1  |
| and questionable reactions.....      | 3  |
| Raw cow's milk.....                  | 1  |
| Rice protein (b).....                | 2  |
| Banana protein (b).....              | 1  |
| Cocoon protein (b).....              | 1  |
| Watery extract of orange (b).....    | 1  |
| Almond protein (b).....              | 2  |
| Almond (crude) (a).....              | 4  |
| Brazil nut protein (b).....          | 2  |
| Brazil nut (crude) (a).....          | 3  |
| Walnut protein (b).....              | 3  |
| Walnut (crude) (a).....              | 5  |

† There is still some doubt as to whether the scarification or the intracutaneous test is the best. There are two points in favor of the use of the scarification test,—its simplicity and the difficulty of interpreting the intracutaneous reactions in some instances. It is probable that the intracutaneous test is the more delicate, as shown by Blackfan. The writer's experiences do not justify the conclusions of Stickler and Goldberg (Jour. Amer. Med. Assn., 1916, lxxi, 349), who considered the reactions positive only when the erythema persisted for 48 hours.

|                                    |   |
|------------------------------------|---|
| Pecan (crude).....                 | 3 |
| Castana (crude) (c).....           | 2 |
| Protoid (crude) (c)*.....          | 1 |
| Hazel nut (crude) (c).....         | 1 |
| Peanut (crude) (a).....            | 1 |
| Potato protein (b).....            | 2 |
| Barley protein (b).....            | 1 |
| Wheat protein (b).....             | 6 |
| Whole wheat flour (crude) (a)..... | 4 |
| Oat protein (b).....               | 2 |
| 12% alc. sol. cat's hair.....      | 2 |
| " " " dog's hair.....              | 3 |
| " " " donkey hair.....             | 2 |
| Horse keratin.....                 | 7 |
| " serum.....                       | 5 |

(a) Crude in this table means that the fresh flour was dissolved as much as possible in cold sterile water or normal salt solution and applied without filtering.

(b) Protein = the protein supplied by Mr. Wodehouse.

(c) In the crude preparation of nuts, the nut was broken, squeezed and some of the expressed fluid placed on the sacrifice.

\* Pinus edulis imported from the southern coast of Italy.

It was found that one individual was apt to react to more than one form of protein, as shown in the case of a child who reacted to egg, lima beans, rice, green split pea, protoid nut, whole wheat, kidney bean, and California pea bean.

The frequency of positive reactions is illustrated by the following figures:

- 6 cases gave only 1 positive skin reaction to different materials.
- 4 cases gave only 2 positive skin reactions to different materials.
- 1 case gave only 3 positive skin reactions to different materials.
- 5 cases gave only 4 positive skin reactions to different materials.
- 2 cases gave only 5 positive skin reactions to different materials.
- 1 case gave only 7 positive skin reactions to different materials.
- 2 cases gave only 8 positive skin reactions to different materials.
- 1 case gave only 9 positive skin reactions to different materials.
- 1 case gave only 10 positive skin reactions to different materials.

It is still too early to say whether all of the positive reactions are of equal clinical importance, but experience seems to show that the severity of the symptoms is not always indicated by the size and character of the reaction. If an individual reacts to one kind of nut he probably will give a skin test to all nuts, except the roasted peanut,\* which is a lentil. It has been found, however, that the severity of the reaction may vary, as, for example, one case which had a marked reaction to the protein of the almond and only a moderate reaction to that of the walnut and Brazil nut. This difference in the reaction may be explained by the difference in the family of the nut. In the same manner, an individual who reacts to the egg of the hen also reacts to the egg of the duck, turkey, buff cochin bantam, English pheasant, pearl guinea hen, Japanese silkie and pigeon. The reaction is, therefore, to the egg and not to the species of the bird. The yolk and the white

\* The heat of roasting the peanut may make it suitable for sensitive individuals.

of the egg each react, but the white usually reacts more strongly than the yolk.

Experience has shown that when a positive skin test is obtained for a food, and the food is then removed from the diet, the general condition of the patient almost invariably improves, and in many instances a cure results. In other instances it is necessary to induce an artificial immunity because of the difficulty in entirely eliminating the offending protein from the diet, as, for example, eggs or milk. Immunity may be induced in these patients by giving increasing doses of the offending protein as described by Schloss.<sup>17</sup>

#### CONCLUSION.

A definite etiological connection may be established between most cases of asthma and some foreign protein by the skin test. If an individual is sensitive to one protein he is also apt to be sensitive to other proteins. The large number of cases with family histories of asthma or food idiosyncrasies makes it seem probable that there is a hereditary predisposition to sensitization. Information given by the skin test is of inestimable value in outlining the treatment of the case, and with the use of this information, marked improvement or cure often follows. Further study will undoubtedly add much to our knowledge of asthma and its allied diseases and will still further modify our conception of the processes involved.

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 Karasawa: *Zeitschr. f. Immunitätsforsch. u. exper. Therap.*, Orig. 1910, v, 509, was able to produce anaphylaxis with extracts of beans, peas, lentils, rice, sago and wheat.

## PREPARATION OF VEGETABLE FOOD PROTEINS FOR ANAPHYLACTIC TESTS.

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In studying the sensitization to various food proteins which results in asthma, eczema, etc., investigators have for the most part used a watery extract or the foods themselves to make the tests. This method, besides being clumsy, has obvious disadvantages, for it is desirable that the proteins of the vegetable foods to be studied should be as concentrated and in a form as easily handled as possible. Chappell ('15), in his studies on asthma, used concentrated extracts of strawberries and tomatoes, prepared by precipitating the watery extract with alcohol, for making the tests.

In the winter of 1915 the writer, without attempting to find out exactly which proteins in the foods were responsible for the biological reactions, endeavored to find a method of concentrating them all together in such a form that they would keep and be easily available for making tests.

It was found that an extract made with pure water would give just as powerful reactions as one obtained by any other solvent, thereby showing that the anaphylactogenic protein is water-soluble or at least soluble in water plus the salts contained in the food. Throughout the subsequent work water was used for extraction. As the work progressed, some of the studies of Dr. J. L. Goodale (as yet unpublished) showed that, as a general rule, vegetable foods, boiled, or moderately cooked in any way, furnished just as powerful anaphylactogens as the corresponding raw foods, thus eliminating, in these, all heat coagulable proteins as possible anaphylactogenic factors. From then on, the watery extracts were prepared from cooked foods, because cooking facilitates the extraction. In the case of the fruits, however, this is not so, for the weight of evidence seems to show that heating destroys their anaphylactogenic properties.

It can readily be seen that no one method could be found which was applicable to all

cases. Indeed it was necessary to study each case separately in order to get the best results; but in general the method employed was to soak the material in as large a volume as necessary (often as much as seven or eight liters to four or five pounds) for several days, using thymol as preservative. After decanting and filtering, the volume was reduced by evaporating before the electric fan at room temperature until the substance became syrupy or gummy. When possible (in only two cases) it was spread on paraffin plates and dried over sulphuric acid, and when thoroughly dry was pulverized in a mortar. Ordinarily, however, it was impossible to evaporate to complete dryness, even by the aid of a desiccator and exhaust pump or by digesting in absolute alcohol, for no matter what the process the product was always a thick gum. So after evaporation the substance was dissolved in sufficient water (as determined by preliminary tests) and precipitated by three or four volumes of 95% alcohol. The precipitate was then centrifugized out and washed through several baths of 95% alcohol, absolute alcohol, and then ether, and finally dried over sulphuric acid. In this way a friable powder was obtained, usually white or still retaining slightly the original color of the vegetable from which it was produced.

It was frequently necessary to deviate from this general plan. For example, it was often advantageous to precipitate with a mixture of acetone and ether instead of with 95% alcohol. When this was done the precipitate was put through two or three baths of this acetone ether mixture, then through ether, and the drying completed over sulphuric acid. It was found also that after precipitating with 95% alcohol the acetone ether mixture could be substituted for absolute alcohol in the dehydration process, the only advantage being that it is rather less expensive.

The powder obtained by this method is not always completely soluble in cold water, though in most cases it goes almost entirely into solution, giving a suspensoid or an opalescent solution. However, if the process of dehydration is delayed and the alcohol left on the precipitate for any length of time the precipitate becomes almost completely insoluble. In consequence, the process, from the precipitation with 95% alcohol, on to the drying in the desiccator, must be hurried over as rapidly as possible. For this reason the precipitates were centrifugized in preference to filtration. If, in spite of all precautions, they become only incompletely soluble in water, they can always be dissolved in weak alkali (about 0.1% KOH), and it has been shown that this strength of alkali does not affect the biological reaction.

For the sake of convenience the preparations made by this method may be classified as follows:

|                   |                       |
|-------------------|-----------------------|
| I. CEREALS.       | IV. ROOTS AND TUBERS. |
| Barley            | Potatoes              |
| Wheat             | Boiled potatoes       |
| Wheat bread       | Baked potatoes        |
| Rye               | Carrots               |
| Corn              | Turnips               |
| Rice              | Beets                 |
| Oats              | Fenestrals            |
|                   | Squash                |
| II. NUTS.         | V. FRUITS.            |
| Almonds           | Apples                |
| Brazil nuts       | Oranges               |
| Walnuts           | Bananas               |
| III. OTHER SEEDS. | VI. LEAVES AND STEMS. |
| Peas              | Spinach               |
| Boiled peas       | Celery                |
| Beans             |                       |
| Cocoa             |                       |

I. *Cereals*: All except rice and oats were treated as described above, and a white powder was obtained almost completely soluble in pure water. It was found that rice and oats could be thoroughly dried on paraffin plates without the use of alcohol or acetone. While the rice preparation could be easily powdered and was completely soluble in cold water, giving an opalescent solution, the oat preparation came out in sheets, not unlike the commercial preparations of gelatin in appearance, and was entirely insoluble in cold water, but would dissolve completely in hot.

The chemical tests showed that in all cases these precipitates were made up largely of protein matter, but in most cases the heat-coagulable proteins were present in small amounts only, the bulk being made up of "proteose" and peptone. Subsequent experiments by the author (unpublished) have shown that, of the two proteoses that can be obtained from wheat flour, one, the natural "proteose" of Osborne ('07, '09) is anaphylactogenic to wheat-asthmatics, while the other, the artificial proteose, obtained by decomposition of the other proteins, is non-anaphylactogenic (cf. also Wells and Osborne, '14, '15).

II. *Nuts*: The large amount of oil present in these nuts was removed by first pressing in a screw-press until no more could be thus removed, then washing through three or four baths of carbon tetrachloride. After the oil was entirely removed and the carbon tetrachloride evaporated off, the resulting meal was treated as indicated above; and in all cases a fine, slightly colored powder was obtained, perfectly soluble. In the case of almonds and Brazil nuts, it was shown by chemical tests to consist largely of protein, but in the case of walnuts the amount of protein was small.

III. *Other Seeds*: Extracts of these are easily precipitated by 95% alcohol, and upon drying a fairly soluble powder is obtained. Chemical tests showed this in all cases to consist largely of protein matter. In the preparation from raw peas an albumin and a proteose could be detected, while in that from boiled peas only a proteose-like body was present.

IV. *Roots and Tubers*: In making these preparations the vegetables were boiled until soft, when they were triturated in the boiling water, plus enough water to make about a liter to .45 kilos, and then allowed to soak for several days. The preparation from raw potatoes was made by grinding up in a meat chopper and allowing to soak in cold water for several days, and the process completed as described above. During the extraction and evaporation, however, the material became jet black, owing to the oxidation of chromogen, and this cannot be removed from the finished product. This difficulty is avoided, however, by using boiled or baked potatoes, because the heating destroys the oxidase, which is the active agent in the oxidation.

Chemical tests show that there is really only a very small amount of protein present in these preparations. The one from raw potatoes showed the presence of a heat-coagulable albumin-like substance and traces of a protein not coagulated by heat, probably the proteose described by Osborne ('96). The cooked potato showed the presence of a proteose or some proteose-like body. The carrot preparation also showed the presence of a proteose-like substance, but in the others no protein could be demonstrated by chemical means.

V. *Fruits*: Great difficulty was experienced here in getting the water-soluble part to precipitate. In the case of bananas, if slightly over-ripe fruit is used, the extract can be made and precipitated in the usual way; but if ripe or under-ripe fruit is used, the ordinary protein precipitants cause a gelatinization of the pectose, which renders it impossible to handle. This same difficulty was experienced with apples and oranges, from which, on this account, no good dry preparation has, as yet, been obtained. At the time of writing these two are still under investigation.

VI. *Leaves and Stems*: These preparations are easily made by the ordinary method. However, in none has any protein been detected by chemical means.

From the foregoing work it was found possible to prepare concentrated watery extracts from all the vegetable foods which are ordinarily responsible for anaphylactic diseases, and put them into an easily available form for making tests.

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## THE NORMAL REACTION OF THE SKIN TO STROKING.\*

## A DESCRIPTION OF THE PHENOMENON, AND AN EXPLANATION OF ITS CAUSATION BASED ON REASON AND EXPERIMENT.

BY EDWARD A. TRACY, M.D., BOSTON.

THE deduction that the phenomenon here described is the normal reaction of the skin to a mechanical irritant is based on the fact that it was observed in 1165 out of 1236 individuals examined. Their ages ranged from six days to 83 years. As there were known disease conditions present in the majority of the remaining cases, it strengthens the deduction that the phenomenon under consideration is the normal reaction.

The phenomenon in brief is this: When the skin of a normal quiescent subject is stroked by a wooden instrument (e.g. a wooden tongue depressor or a match) it reacts by a deepening of the skin tint, generally brief in duration, appearing where the stroke was made, or in its immediate vicinity, and then, after a period of about fifteen seconds, by a longer lasting whitish color (in Caucasians), showing itself in the location where the stroke was made. The reaction is seen most clearly when the test is made for it on the rosy cheek of a healthy Caucasian boy or girl. The cheek is stroked across, lightly, once; its tint where stroked is soon seen to deepen, and, after a while, fifteen or more seconds, a pallor takes the place of the redness, the streak of white being very noticeable because of its contrast with the rosy field on which it is displayed. The normal reaction just described consists then of two components, the one, vaso-dilation, and the other, vaso-constriction.

## THE CAUSATION OF THE ABOVE-NOTED PHENOMENON.

Besides the normal reaction described, and consisting of two components—vaso-dilation and vaso-constriction, reactions were obtained in subjects in which one of the components was absent; that is, cases were tested in which no vaso-dilation occurred, the vaso-constriction component being present alone in response to the testing stroke, and other cases were tested in which the vaso-dilation component alone was present.

There must be some cause or causes for such various reactions to the same irritant.

It is assumed that the reactions of vaso-dilation and vaso-constriction of the blood vessels of the skin, originate in nerve stimulation caused by the mechanical irritation of stroking.

To produce the reaction a nerve mechanism is assumed for the reacting blood vessels, similar to that given graphically by Rudzki-Hornowski,<sup>2</sup> and based on the work of Ranvier, Schiff and

Gianuzzi; their diagram illustrating the connection of the local fibrils and ganglia of the sympathetic nerves with the blood vessels at the periphery. It is assumed that this is modified somewhat to allow for a connection with the sensory filaments of the skin, and with the autonomic nerve fibres, that are assumed to be in all of the integument as they are known to be in the integument of the face. This latter connection permits of central stimulation of the mechanism of vaso-dilation.

It is assumed that fibres from both branches of the vegetative nervous system,—the autonomic and the sympathetic,—such as are described by Rudzki-Hornowski<sup>2</sup> as an actuality for the sympathetic system, reach into the intima of the blood vessels.

Now the nerve mechanism, whatever it may be, is manifestly the same in all the subjects tested. One thing, however, reached by this mechanism—the blood—is all important, and it is assumed to be a part of the mechanism concerned in the phenomenon observed. The fact that the sympathetic nerve fibrils reach into the intima, that is, that the nerve mechanism of vaso-constriction is known to come into contact with the blood, is a basis for assuming the blood to be a part of the mechanism. It is thus considered a physical part of the mechanism, just as the vessel's walls are, both being in intimate contact with the nerve fibrils which communicate with near-by ganglia.

As has been said, the nerve mechanism is manifestly the same in all the subjects tested. There is one element in the assumed mechanism, however, that is changeful in every case tested, and that element is the blood continually flowing through the vessels and bathing the ends of the vaso-motor nerves in the intima of the vessels. Besides changing constantly its position, it is changeful in composition, carrying the hormones, activators to various organs, and also the various products of metabolism. It is natural therefore, to look to the blood—the only changeful element in the mechanism under consideration—for a solution of the riddle of the reactions found to occur,—the reaction of vaso-dilation followed by vaso-constriction, as the result of a single stroke irritation, the reaction of vaso-dilation alone in some cases, and the reaction of vaso-constriction alone in other cases.

Mention has been made of the fact that hormones, activity incitors, are carried in the blood stream. These are substances given to the blood streams by the endocrinous glands. They are less complex than albumen, and capable of ready osmosis through animal membrane.

We know that adrenalin, one of them, is an activator of sympathetic mechanisms. Polak,<sup>3</sup> from his experiments on glycosuria production, concluded that adrenalin works by acting on the peripheral endings of the sympathetic. We know that this hormone is being constantly supplied to the blood stream.

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I have observed, after the therapeutic injection of adrenalin in cases in which, before the administration of it, the vaso-constriction component of the normal reaction to stroking was absent, that after about five minutes, on testing, the vaso-constriction component appeared. This can be explained only by the adrenalin added to the blood stream activating the vaso-constriction mechanism by acting on the peripheral endings of the sympathetic nerve in the intima, its activation being evoked by the irritation of stroking. Here, by direct experiment, Polak's deduction that adrenalin acts on the nerve-endings of the sympathetic is visibly verified.

Thus we have one hormone, adrenalin, with a known incitor action of the mechanism of vaso-constriction. But the phenomenon cannot be explained by this hormone alone. We are obliged to assume the presence of at least two hormones in the blood to produce the three reactions that have been observed: 1, vaso-dilation, brief, followed by a slow-coming vaso-constriction that is comparatively long lasting—the normal reaction; 2, the reaction observed in which vaso-dilation alone occurs; and 3, the reaction observed in which vaso-constriction alone occurs.

We cannot suppose the activation of these reactions to be due to the known hormone adrenalin alone, its presence causing its known action of vaso-constriction on the vaso-motor mechanism and its absence causing vaso-dilation to occur; that would account for but two of the reactions noted above, leaving unexplained the normal reaction, the one most frequently observed,—the reaction of brief vaso-dilation followed by slow and long-lasting vaso-constriction sequential to a single stroke of mechanical irritation.

Therefore two hormones at least are necessary for the causation of the phenomena observed.

Moreover, to explain the phenomena, a nerve mechanism for vaso-dilation is necessary, together with the one generally allowed to exist for vaso-constriction. In other words, the vaso-dilation observed is not due to a mere temporary paralysis of the vaso-constriction mechanism. Let us assume that there is only one nerve mechanism,—the known one of vaso-constriction. It has already been shown that two hormones are necessary to explain the phenomena observed. If both hormones are present in the blood of the vessels and activate the same nerve mechanism, it is difficult to see how the normal reaction could occur unless we assume that the paralyzing hormone acts for a brief time only, being always overcome by the activation of the adrenalin on the mechanism. In the absence of adrenalin, the activation of the paralyzing hormone, evoked by irritant or stimulus, could be long lasting, and account for the sole vaso-dilation reaction to the irritant stroking sometimes observed. But the assumption that there is only one nerve mechanism—the sympathetic—would

not allow for the central origin of stimuli to produce vaso-dilation, because experimental central irritation of the sympathetic fibres never produces vaso-dilation; that is, central stimulation or irritation of the sympathetic fibres always activates the mechanism only in one way, that of vaso-constriction.

Hence the activation of vaso-dilation by central stimulation requires a nerve mechanism for its production independent of the sympathetic mechanism.

If, however, we assume a double nerve mechanism connected with the blood vessels in the skin to be present, a ready explanation of all the phenomena observed is offered.

With a double nerve mechanism we can understand how both could be activated by a single stroke of mechanical irritation. In the presence of the incitor hormones,—hormone X for vaso-dilation, and hormone adrenalin for vaso-constriction,—both nerve mechanisms could be activated at once, and quick and brief vaso-dilation, and slow and long-lasting vaso-constriction occur. If the hormone X—incitor of vaso-dilation—were present alone we should have a strong vaso-dilation reaction as a result of the stroke of irritation. If the hormone adrenalin—incitor of vaso-constriction—alone were present, we should obtain activation of the vaso-constrictors and it would be long lasting.

Such are the phenomena observed, and it appears rational to predicate a double nerve mechanism, one for vaso-dilation and one for vaso-constriction. Otherwise, as has been shown, the normal reaction observed and described cannot be explained.

This theory of a double nerve mechanism of the peripheral blood vessels is also in accord with the facts of central stimulation of certain autonomic nerve fibres causing vaso-dilation of the face, and central stimulation of the cervical sympathetic, causing vaso-constriction of the same region.

As corroborative of this theory of a double nerve mechanism for the blood vessels of the skin, I regard the observations of Meltzer,<sup>4</sup> who noted that stimulation of the vagus [autonomic] produces only a brief after-effect, while stimulation of the accelerator nerve [sympathetic] leaves a long-lasting after-effect. In the phenomenon of the normal reaction described—the vaso-dilation, assumed to be due to stimulation of autonomic fibres, is of brief duration; and the vaso-constriction, due to stimulation of the sympathetic, is long lasting.

As further corroboration of this theory of a double nerve mechanism of the blood vessels of the skin, I here report an experiment of injecting pilocarpine into the skin. Eppinger and Hess,<sup>5</sup> together with other German investigators, have found this drug to be the analogue of the physiological hormone X (or "autonym") as they term the hormone) as an incitor or activator of the autonomic nervous system only.

The injection of pilocarpine into the skin was followed by quick vaso-dilation locally and the production of a wheal formation apparently identical with *urticaria factitia*. In other words, pilocarpine, a known activator of autonomic nerve mechanisms, activates a nerve mechanism in the skin that is not the sympathetic mechanism.\* The conclusion is it must be the autonomic nerve mechanism really present in the skin. I have already described an original experiment demonstrating that adrenalin activates the sympathetic nerve mechanism of the blood vessels of the skin.

To recapitulate briefly: The phenomenon observed and here reported of the normal reaction of the skin to mechanical irritation produced by stroking with a wooden instrument, and consisting of vaso-dilation, brief in duration, followed by vaso constriction, long lasting, the writer holds is caused by a double nerve mechanism, one for vaso-dilation (autonomic) and one for vaso-constriction (sympathetic); together with at least two hormones in the blood stream, the hormone X (Eppinger and Hess' "autonomyn") activating the vaso-dilation mechanism; the other hormone, adrenalin (or analogue, inciters of sympathetic nerve endings), activating the vaso-constriction nerve mechanism.

#### COROLLARY.

The clinical examination of a patient should include testing for the above described reaction. If both components of the reaction are present, the normal reaction, we know then that the hormones activating the autonomic and sympathetic branches of the vegetative or visceral nervous system are present in the blood. If the vaso-dilation component alone is present we know that the hormone X, or analogues, are in excess in the blood, or that the hormone adrenalin (or pituitrin with analogous action), is in insufficient amount to activate the sympathetic nerve endings in the blood vessels tested. If the vaso-constriction component alone is present, we know that the hormone adrenalin (or analogue) is present in excess in the blood, or the hormone X, or analogues, are present in insufficient quantity to activate the autonomic fibrils in the blood vessels.

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\* The vaso-dilation caused by the pilocarpine is not due to paralysis of the vaso-constriction mechanism, because stroking (with a blunt pin) results in a streak of vaso-constriction in the reddened area.

## PROTEIN EXTRACTS IN STATES OF HYPERSENSITIZATION.

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ANDERSON and ROSENAU in their Harvey lecture define hypersusceptibility as a condition of unusual or exaggerated supersensitiveness of the organism to foreign substances. The term anaphylaxis is similarly used. Numerous observations, extending over a period of years, have been made both on animals and human subjects in regard to the supersensitive state and its relation to various foreign substances.

Clinically, one of the best known examples of anaphylaxis is the hypersusceptibility to pollen showing itself as hay fever. The reactions produced by tuberculin and mallein in suitable individuals are well recognized examples of this phenomenon.

More recently, as the result of much clinical and laboratory work, certain other clinical conditions have lately been grouped as anaphylactic states, notably poisoning following the ingestion of strawberries, fish or eggs, and showing itself by gastro-intestinal manifestations.

In like manner, also, not only the well recognized pollen fever, but rose cold and the condition known as bronchial asthma, come under this head. This latter clinical entity differs somewhat from other hypersensitive states in that there may be several sensitizing factors present playing a definite part in the production of the disease; so that at the present time it would seem possible not only to have various food products playing a part, but also numerous bacterial proteins.

Von Pirquet, from his study of vaccinia and the local reaction produced by the injection of tuberculin, showed that sensitization could be estimated from the local phenomena taking place about the point of inoculation.

Since the development of the so-called von Pirquet test for tuberculosis this method is now extensively used to test states of hypersensitization to various proteins, bacterial and otherwise. While other methods, such as the eye reaction of Calmette in tuberculosis and the use of products of autolysis of the typhoid bacillus distilled into the eye to detect typhoid fever, have been extensively used, for all practical purposes the simpler cutaneous test is the most practical method.

To carry out this test for the detection of hypersusceptibility towards various proteins the preparation of extracts is of considerable importance. In order to get the best results it is essential that the preparations used should readily be held in suspension, should be sterile and should be suspended in a non-irritating and readily absorbable diluent. Where bacterial proteins are under consideration, pure cultures must be secured, free from the media

used, and identification, not only of the type, but of the group of organisms to which they belong, should be complete.

In attempting to devise a method to prepare protein extracts from bacteria or foods, many difficulties have arisen. The first obvious step, however, was to avoid the use of chemicals which would neither form insoluble compounds with the protein present, nor form compounds which might lead to erroneous results. Furthermore, the use of excessive heat may to a considerable degree impair the solubility of some proteins. Desiccation to dryness of a substance requires a considerable period of time, and the use of various extractives offers the opportunity for more or less modification of the material from its original composition.

The following methods have been used:

The frequency with which local reactions take place at the point of inoculation in the use of bacterial vaccines at once suggested the method of Wright as one which could be employed in this work.

Various bacteria grown in pure culture in abundance were suspended in normal salt solution and killed by 60° of heat for 30 minutes. Heavy suspensions were than used to detect sensitization. This method, while simple and relatively quickly carried out, has the objections that the final product is inconstant in its concentration, and the prolonged action of heat may materially modify the protein to be tested.

A second method was that of securing a heavy suspension of a bacterial growth, or of food, in salt solution, centrifuging to produce concentration, and then obtaining the substance, bacterial or otherwise, in a dry form by successive washings with alcohol and ether. A suspension of 5 mg. of the residue in one cc. of 15% alcohol was then prepared. The comparison of these suspensions with others later used showed that these preparations were less soluble and reactions were less readily obtained.

Several modifications of this method were carried out, such as the addition of acetone to the original solution to throw down the suspended protein; the use of 0.5% solution of phenol with  $\frac{1}{20}$  normal sodic hydrate as solvents to the precipitated protein; and the autolysis of various bacterial suspensions under ether vapor, followed by extraction with alcohol and ether. The direct application of the resulting powder to the skin was then made.

All these methods were found to be unsatisfactory in that the extracted protein gave unreliable results or failed to show a reaction where sensitization was known to be present.

The above methods, though unsatisfactory, clearly demonstrated the necessity of obtaining the protein extract in a soluble form and of such strength as to render it possible to show a cutaneous reaction, where food or bacterial sensitization is present.

On account of the great variety of food

products which may give rise to sensitization, some variation in their preparation is necessary. In general the following method is equally applicable to both food and bacterial preparations.

The material to be used is secured in large quantities and suspended in normal salt solution with 0.5% phenol added. A bacterial suspension is autolyzed at a temperature of 48° for 24 to 72 hours, depending upon the organism in suspension. During this process the cellular structure of the organism is more or less completely broken down.

The suspension, immediately following the period of autolysis, is quickly evaporated to dryness by a constant temperature of 40°, thus favoring the reduction of the protein to a soluble form. This latter step is carried out by the following simple device. The suspension to be evaporated (this applies to all protein extracts) is placed in flat bottomed glass dish, over a water bath, with an air current from an electric fan directed over the suspension. The flame under the water bath is protected by a shield to prevent variations of temperature. By this simple device the temperature remains constant and quick evaporation to dryness is obtained.

The evaporated material is collected and is kept free from contamination by immediately transferring the preparation to sterile glass-stoppered bottles and sealed. For testing purposes the powdered extract is ground up with glycerine in the proportion of 10 mg. of the powder to 1 cc. of glycerine. One to two drops of this preparation are used for a test. If the powder is applied to the skin directly a constant standard cannot be established or a sterile preparation cannot be vouched for. The glycerinated preparation insures, with ordinary care, a sterile preparation and a constant strength, thus establishing a standard.

The test is carried out in a similar way to the von Pirquet tuberculin test. The inner side of the forearm is cleaned with alcohol and ether, and two scarifications or similar scratches are made about three inches apart, allowing the oozing of serum only. On one spot or scratch one or two drops of the extract are placed and allowed to soak in. The other spot is kept as a control. Both spots should be examined at intervals of twenty minutes, half an hour and one hour. In many cases the food extracts give quicker reactions than the bacterial extracts. Positive reactions consist of a raised urticarial wheal, surrounded by an area of redness of the skin, somewhat circular in outline and usually from 2 to 7 mm. in diameter.

The possibilities of such a method to determine hypersensitization are far reaching. For example, in such a condition as bronchial asthma, one or more factors may play a part in the sensitization so that a large series of tests may be necessary in order to determine all the factors involved. A detailed history is essential as

well as various skin tests with pollens, food and bacterial extracts. Some such outline as is given below may help to bring out many of the factors concerned in a complicated case.

#### CHART.

Symptoms following:

(a) Inhalation of:

1. Grasses, ragweed, goldenrod, asters, etc.
2. Animal products of: horse, cat, guinea pig, etc.
3. Chemicals, dyes, dust.

(b) Ingestion of:

1. Grains.
2. Nuts.
3. Fruits.
4. Molluscs.
5. Meats.
6. Milk.
7. Eggs.
8. Fish.

(c) Infection with:

1. Staphylococcus group,—aureus, albus citreus.
2. Streptococcus group,—Pyogenes, fecalis, anginosus.
3. Pneumococcus group, types 1, 2, 3, 4.
4. Diphtheroid group.
5. Bacillus influenzae.
6. Micrococcus catarrhalis.
7. Friedlander group.
8. Bacillus ozaenae.

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### Clinical Department.

## HAY-FEVER: ITS TREATMENT WITH AUTOGENOUS VACCINES AND POLLEN EXTRACT.

By LEON S. MEDALLIA, M.D., BOSTON.

#### INTRODUCTION.

This paper is a report of six cases of hay-fever (5 autumnal and 1 June hay-fever) treated with autogenous vaccines. The symptoms in the autumnal cases usually began about the middle of August and would last until late

in November, being relieved after the second or third heavy frost. Five of the six cases have been seen by me for the first time during the attack last year, while the sixth I had under observation since 1911, at which time she applied for treatment for alveolar osteomyelitis or "pyorrhea." The treatment and relief from the hay-fever in this last case was incidental. The extent of time this patient was under observation (5 years) is of value in the discussion of a seasonal disease such as hay-fever.

#### ETIOLOGY.

Pollenosis as being the direct exciting cause of this disease is by this time fairly well established. The direct production of typical attacks of hay-fever at any season of the year by having the patient inhale pollen, as reported by Scheppegrell,<sup>1</sup> is in my opinion more valuable as a means of establishing the etiologic relation of pollenosis to this disease as well as a means of diagnosis than the cutaneous reactions so extensively carried on by Goodale<sup>2</sup> for almost any kind and variety of proteins.

The specificity of intradermal and cutaneous reactions has been greatly undermined by the work of numerous investigators as quoted in two recent articles by Stokes<sup>3</sup> and by the investigations carried out by Stokes himself.<sup>4</sup>

The subject of cutaneous reactions is a very complex one, and really embraces the whole problem of the physical mechanism of anaphylaxis, and is entirely beyond the scope of this paper. That much is, I believe, sufficient for our purpose;—that these cutaneous reactions are not due to any specific antigen-antibody reaction; they can be elicited by inert substances such as agar, bismuth subnitrate, etc., and are, therefore, of little diagnostic value.

The wholesale empirical application of the cutaneous tests or "skin scratches" in vaso-motor disturbances will prove, I believe, of very little value, if any, as a diagnostic measure. The attempt to substitute a cutaneous reaction, elicited by bacterial extracts,<sup>4</sup> for bacteriological and cultural findings seems to me entirely unwarranted, more especially in such cases where cultures are obtainable and the infecting organism easily determined.<sup>†</sup>

\* The mechanism of the cutaneous reaction is now held, by practically all investigators on the subject, to be due not so much to the substance introduced parenterally, as to the released ferments normally present in the individuals—released by the adsorbing action on the anti-ferments by the substance introduced parenterally. Whether the substance be ragweed extract, bacterial extracts, egg albumen, horse keratin, lentin, tuberculin or plain agar matters very little since "cutaneous" reactions can be obtained in apparently healthy individuals with any of the above-named substances for no apparent reason. Why such reactions should occur in some normal individuals and not in others has not been worked out as yet.

† Further investigations will, I believe, disclose that the reason for these skin reactions is due to the general hypersensitiveness of the skin of these individuals, similar to the hypersensitiveness of their mucous membranes associated with it, as well as a state of lowered coagulability of the blood. Thus the state of the individual, rather than the particular substance used in the test, will be found underlying the reaction.

The reaction to the bacterial extracts as described by Goodale,<sup>4</sup> lasting from ½ to 1 hour without going on to pupule formation, is, I believe, no reaction at all, since the artificial tendency of the skin of such individuals may be sufficient cause for such a transient reaction caused by a "scratch" and the introduction of any substance that would act as an anti-ferment adsorbent.

The mechanism of the production of hay-fever in the light of these new developments concerning the physical mechanism of anaphylaxis could, therefore, be considered as being due to:

First. The pollen-albumens adsorbing the anti-ferments, thus allowing the natural ferments present in the nasal secretions, mucous membrane, lymph and blood to produce the anaphylatoxin, which, in turn, causes the well-known symptoms of hay-fever.

Second. The bacteria present in the nose are thus enabled to cause infection, aggravating and keeping up the condition which would otherwise have been a slight transient affair. I have already referred to a similar phenomenon in a previous article,<sup>8</sup> in connection with eczema, where the direct exciting etiologic factors responsible for what would otherwise be a *passing dermatitis* produce a true eczema because of the superimposed infection with the staphylococcus aureus.

Third. The lowered coagulability of the blood of the individual and the consequent dilated superficial capillaries make it easy for any substance to provoke anaphylactic symptoms.

The principal factor in the etiology, namely, pollenosis, is the most important exciting cause in this disease. I feel that only such pollens can produce the disease which, when lodged upon mucous membranes of susceptible individuals, are capable of being attacked and their albumens liberated by the secretions of such mucous membranes. The albumens thus set free adsorb the anti-ferments and allow the normally present ferments (when freed from the inhibitory action of the anti-ferments) to cause toxicity with the production of the well-known symptoms of hay-fever. The mechanism of the natural production of this disease—the adsorption of the anti-ferments—is the reason why one attack makes the individual more susceptible rather than immune to further attacks. For this reason no therapeutic immunization could be expected from the local inhalation of pollens, as Scheppegrell<sup>1</sup> reports having used, or from the subcutaneous administration of pollen extracts. No other more plausible explanation has as yet, in my opinion, been brought forward that would satisfactorily explain the symptom-complex of this disease.

The bacterial relation to this disease cannot be so easily put aside as Scheppegrell<sup>1</sup> would have us do. The constant presence of abundant staphylococcus albus, aureus or citreus, either alone or in combination, in the nose as well as in the conjunctival secretions, in all my patients who returned this year for prophylactic inoculations while in their normal state, is certainly of significance. The vast number of negative cultural findings of the nasal secretions I have personally obtained in patients who applied for various diseases, other than hay-fever, and without any nasal infection, makes me feel that there is a definite rela-

tion between the bacteria isolated from the nose and this disease.

It is true that the bacteria are there without causing the symptom-complex; they cannot, therefore, be referred to as the exciting cause of this disease; their presence, however, is abnormal, and may be the cause of the lowered local resistance preparatory to pollenosis. The bacteria and their products are also probably responsible for making it possible for the conjunctival and nasal secretions to attack the pollens, liberate their albumens and cause the disease.

Thus the presence of the bacteria and their products are, I believe, the deciding factors between individual's being susceptible to the disease or not; while the superimposed infection which these bacteria cause, following the anaphylactic state (sneezing) due to the pollenosis is, I believe, responsible for the real symptoms of the disease, changing it from a mere transient sneezing spell to a real disease with considerable suffering.

I cannot explain in any other way the startling results obtained in this disease, by myself and by others as found in the literature, with the use of autogenous vaccines. The bacterial element in this disease is, therefore, I believe, of great importance.

The lowered coagulability of the blood is the principal reason why good results have been reported by the use of calcium chlorid in the disease under discussion. This drug, as is well known, raises the coagulability of the blood, making it considerably more difficult for the blood serum to ooze out from the capillaries upon the slightest provocation, as is the case otherwise.

#### BRIEF REVIEW OF THE LITERATURE.

I shall not enter upon a discussion of the results obtained by means of pollen extract or pollen serum administration in the various forms, as found in the literature. From our knowledge, as already referred to, of the mechanism underlying anaphylatoxin production and its consequent symptoms by means of the pollens, it would seem to me that theoretically no success could be hoped for from the pollen extract administration because the pollens produce in nature anaphylaxis and not infection followed by immunity, as bacteria do. Our present-day knowledge of the results of such treatment substantiates my contention. Thus Scheppegrell,<sup>6</sup> who was one of the first men in this country to use and report the pollen "immunizing treatment of hay-fever" in 1909, states in his latest article<sup>1</sup> (March, 1916) that the method was gradually discontinued. The only thing he has to offer, now, for this disease is the preventive treatment by means of the eradication of the various pollen-bearing weeds.

I shall now refer briefly to the results obtained with bacterial vaccines in the treatment

of this disease, as found in the literature. Farrington<sup>7</sup> reports 25 cases treated with autogenous vaccines made up from the bacterial growth obtained from the nose after the symptoms have developed. Out of the 25 patients thus treated, he reports 13 cured, 8 of whom were complicated with asthmatic attacks; 6 were markedly improved, 5 of whom had asthma; 3 slightly improved, all had asthma; and 3 failures, all had asthma. He concluded that "autogenous vaccine offers decidedly more in the treatment of hay-fever than all other methods combined."

Morrey<sup>8</sup> reported 8 cases treated with autogenous nose vaccine, with relief in all.

Strouse and Frank<sup>9</sup> report 13 cases (5 early June fever and 8 autumnal fever) treated with autogenous nose vaccine. Of the 5 with June fever, 2 were cured, 2 were slightly relieved, and 1 greatly relieved; of the 8 cases with autumnal hay-fever, 4 were greatly relieved, 2 relieved, and 2 no effect.

They report 3 cases that have been free from hay-fever until a hot spell in September, at which time these patients had a very severe attack. Most surprising results were obtained, they say, by the administration of autogenous vaccines, the symptoms almost completely disappearing following the first injection. A similar result was obtained in a fourth case. In all these four cases seasonal cures were obtained.

These authors conclude that, of the two methods of treatment, the autogenous vaccines seemed to have given "equal or better results in individual cases," as compared with the results obtained from the use of pollen extract.

#### PERSONAL WORK.

The cases I had under observation were all treated with autogenous vaccines obtained from the nose and throat. The cultures were obtained by passing a sterile swab along the floor of the nose to the posterior wall of the pharynx, being careful to swab off, in withdrawing, the mucous lining of as much of the passage as possible. Cultures are then made in the ordinary way on glucose agar, blood serum, bouillon and blood agar. Several tubes of glucose agar slants are used, sufficient for an auto-vaccine. Cultures are made in a similar way from the throat by swabbing off tonsils and going in as deeply as possible between the pillars of the fauces. Cultures from the eye conjunctiva are made by placing a swab on the cornea toward the inner canthus, covering it up with the lids and having the patient squeeze the lids tight,—the swabs soak in any of the secretion present,—then having the patient release the lids and the swab is removed. The growth, as a rule, was found sufficient at the end of 24 hours for the preparation of the autogenous vaccines,—which is carried out in the ordinary way.

Four of the cases were treated with pollen ex-

tract alongside of the autogenous vaccine. The results obtained, however, in the cases treated with the autogenous vaccine alone, as well as in the four cases treated by the combined method, from the way these same cases reacted to the autogenous vaccine prior to the use of the pollen extract, makes me feel that the pollen extract can be easily dispensed with.

Four of the autumnal cases were seen for the first time during the attack, while the fifth one came in three weeks prior to his usual time of attack. All the five cases with the autumnal fever have been relieved from the hay-fever by the autogenous vaccine for the first time in several years, and can be considered "seasonal cures."

The one early June fever (Case 1) I had under observation since March, 1911, and I believe it is the only case of hay-fever on record on whom autogenous vaccine has been used for that length of time.

The hay-fever in this case has always been accompanied by asthma and has been of over 20 years' standing. The relief in response to the autogenous vaccine was marked, necessitating two to three treatments each year, with no discomfort to the patient. She has had no asthma practically from the beginning of treatment, and with the exception of a slight transient attack of sneezing following a long auto trip, she has been free from hay-fever. She has had no recurrence this year (1916).

No pollen extract has been used in this case, nor did I feel justified in trying anything else, since her autogenous vaccine has given such good results.

This case has been the stimulus of my other cases, and although I have used, in some of the others, the pollen extract alongside of the autogenous vaccine, I feel that the latter is the more important therapeutic agent in this disease.

Probably the best way of presenting the results of this treatment will be by a brief résumé of each case history.

CASE 1. N. W. J. Female, 50 years, March 22, 1911.

*Family History.*—Mother had hay-fever; otherwise negative.

*Past History.*—Negative.

*Present Illness.*—Applied for treatment for advanced alveolar osteomyelitis (pyorrhea); has three loose teeth and lost several from looseness. Has hay-fever and asthma, which begins regularly in June and lasts, as a rule, for six weeks every year; has had it for over 20 years. Cultures from nose showed staphylococcus (weak) aureus. She received ten treatments with autogenous vaccine, ranging in doses from 150 to 200 million at an interval of 5 to 14 days, July, 1911, is feeling well; gums very much improved; "has had no hay-fever this year; is very much delighted over it."

Returned on May 28, 1912, with a slight sneezing attack; "feels hay-fever coming on"; was given an injection of vaccine on the same day and another one on June 8 and June 13; responded very well; hay-fever has not developed. Was again seen

on June 2, 1913, when she came in complaining of "hay-fever coming on following a long auto drive"; received a treatment the same day and another June 9; "has had no asthma the 17th of June, the first time in 20 years; has felt fine and free from hay-fever"; received another inoculation on June 24 and July 9. Was again seen on June 12, 1914, "slight sneezing and hay-fever coming on"; hay-fever has not developed much. Was again seen on June 14, 1915. "Has been free from hay-fever three weeks over this year. Just began to sneeze slightly"; otherwise well; was given 150 million autogenous vaccine. Another treatment on July 6 and July 14. Has been well since; free from hay-fever this year, 1916.

CASE 2. B. M. G., 49 years, male, merchant. July 23, 1915.

*Family History.*—Hay-fever and asthma on mother's side; has an uncle that is suffering from asthma.

*Past History.*—Has had all sorts of children's diseases; otherwise negative.

*Present Illness.*—Complains of hay-fever of 37 years' standing; begins as a rule on the 19th of August and lasts until after the second or third heavy frost, usually is suffering up to the end of November; has used pollantin, with no benefit; has had a variety of treatment by various physicians without any results. Cultures from nose showed staphylococcus aureus and albus. Throat cultures showed strepto-pneumo and M. catarrhalis. Autogenous vaccines were made from the nose and throat cultures. He was tested to daisy, tansy, goldenrod and ragweed; was found positive to goldenrod and negative to the others.

He received 12 injections of his autogenous—nose and throat—vaccines, ranging from 250 to 500 million, at an interval of 3 to 5 days. He also received four inoculations with goldenrod extract, beginning Sept. 11, alongside of the autogenous vaccines.

This patient, aside from a slight attack of sneezing following a long auto trip (on Sept. 1), was free from hay-fever for the first time in 37 years. He was discharged Oct. 9, 1915, feeling very happy over the results obtained with the autogenous vaccines. He is coming back the middle of July for prophylactic inoculations. This case can be considered a "seasonal cure." The four inoculations of goldenrod extract I do not believe had much influence upon the outcome.

CASE 3. K. F. C., 39 years; male; letter-carrier. August 23, 1915.

*Family History.*—Negative to hay-fever.

*Past History.*—Had scarlet fever when a child, accompanied by a serious eye trouble; got over it; has had no serious illness.

*Present Illness.*—Hay-fever and asthma of 22 years' standing; has had the hay-fever for about a week now; has had the asthma for a week previous to that; does not have asthma unless it comes with the hay-fever. Nose markedly swollen, completely clogging up passages; whole pharynx edematous and inflamed. Has had an operation on the nose some years ago, with no relief; was tested to ragweed, goldenrod and daisy; was found markedly

positive to ragweed and negative to the others. Cultures from nose showed a growth of an unidentified bacillus, and a diplococcus from which an autogenous vaccine was made up. He received 200 million of the autogenous vaccine on August 30; had a severe reaction following it; his asthma and hay-fever very much worse that night; was better the next day. Sept. 3 he received half of the previous dose, which was followed six days later by another dose similar to the first; three days after the third inoculation (Sept. 12) his hay-fever and asthma cleared up. He received four more prophylactic treatments at an interval of one and one-half to three weeks, and was discharged cured (Nov. 2) with directions to return next year, a month prior to the time when his hay-fever is due.

This patient was a great sufferer from the hay-fever and asthma,—the most pronounced case I have seen, of 22 years' duration. The way he responded to the autogenous vaccine cannot be emphasized too strongly. He received no ragweed pollen extract. He has been attending to his work all along throughout treatment, and although he has been exposed to considerable ragweed on vacant lots while delivering the mail on his tours, three or four times daily, he has not had any return of his trouble, and can be considered a "seasonal cure."

CASE 4. P. R. F.; age, 51 years; clergyman, Sept. 13, 1915.

*Family History.*—A brother has always had asthma and hay-fever in England; otherwise negative.

*Past History.*—Has been practically well all his life, except for "colds"; has had "continuous local treatment with some spray or other"; had a streptococcus sore throat about two years ago, which affected his leg, suffering considerably.

*Present Illness.*—Hay-fever, definitely pronounced for last three years; previous to that he thought it was just a "cold." Chief complaint is inflammation and itching sensation of the eyes; sneezes considerably; nose gets markedly stuffed up; has to breathe through his mouth; was well while he was up in the mountains; began to be troubled on train on his way home a few days ago. Was tested to ragweed, goldenrod and daisy; was found positive to ragweed and negative to the two others. Cultures from nose showed staphylococcus albus and few streptococci; cultures from throat showed streptococci and pneumococci. Autogenous vaccines were made up. He received five injections of autogenous nose and throat vaccine, ranging in doses from 250 to 750 million, at an interval of two to seven days. Each vaccine inoculation was accompanied by increasing doses of ragweed extract in the opposite arm. There was a very marked improvement in symptoms following the second inoculation, and he was well after the fourth treatment (10 days after the beginning of treatment); was given a prophylactic inoculation on Oct. 1 and another on Oct. 13. Discharged, cured as to hay-fever.

This patient has been very happy over the results obtained in his case with the autogenous vaccine. It remains an open question as to the

benefit derived in this, as well as in the next two cases, from the use of the ragweed extract alongside of the vaccine. I hope to be able to settle definitely this question in a future article. It will be interesting to see how he will fare the coming season.

This patient returned June 8, 1916, for prophylactic inoculations before leaving for England. Has been especially well this winter and is feeling fine now.

CASE 5. C. K. E.; male; 22 years. Sept. 18, 1915.

*Family History.*—Father had hay-fever for the last few years; one brother has hay-fever.

*Past History.*—Negative except for "colds" since he has grown up.

*Present Illness.*—Complains of hay-fever; has had it for the last 12 years; comes on usually in the middle of August, lasts until some heavy frosts appear; has had asthma with it for the last three years. No asthma without the hay-fever, and only at night; was quite bad the last few days; had nose operation; spur removed last summer; had his tonsils removed when he was nine years old. The nose operation has not proved of much benefit to the hay-fever; going near horses bothers him a great deal. Was tested to ragweed, goldenrod and daisies; was found positive to ragweed; negative to the others. Cultures from nose showed staphylococcus albus and citreus.

He received six treatments of autogenous vaccines ranging in doses from 50 to 150 million at an interval of 5 to 14 days. He was given at the same time, in the opposite arm, gradually increasing doses of a 1% ragweed extract solution, beginning with min. 3 up to min. 20.

This patient showed a marked improvement following the first inoculation of his autogenous vaccine, and was free from both the hay-fever and asthma following the second inoculation on Sept. 25. All further treatments were more in the nature of prophylaxis. Was discharged well and told to return a month prior to his usual hay-fever season. He showed a very marked improvement generally and was very happy over the result.

This patient returned June 10, 1916, for prophylactic treatment, feeling very well. Cultures from nose showed a very profuse growth of staphylococcus, citreus and albus. A similar growth was present in cultures from conjunctival secretions from which autogenous vaccines were made. He will be followed up with prophylactic inoculations of his autogenous vaccines without the ragweed. The results will be reported upon in a future paper.

CASE 6. B. W. H.; female; 37 years. Sept. 27, 1915.

*Family History.*—Negative.

*Past History.*—No serious illness except "colds" and sore throats. Has had hay-fever for the last 15 years; begins as a rule on the 16th of August and lasts to the end of November. Went to Bethlehem and felt no relief; has had considerable

stomach upsets for the last two months; lost 12 pounds; is feeling miserable.

*Physical Examination.*—Negative, except for inflammation of the throat, marked inflammation and edema of the nose. Cultures from nose showed staphylococcus (weak) aureus and diphtheroid bacilli, from which an autogenous vaccine was made; she was tested to goldenrod, daisies and ragweed; was found markedly positive to ragweed and negative to the others.

She received seven treatments with autogenous vaccines, ranging in doses from 100 to 250 million, at an interval of 5 to 7 days. She was also given gradually increasing doses of ragweed extract in the opposite arm, receiving 8 inoculations of a 1% solution, ranging in doses from min.  $\frac{1}{4}$  to min. 6 of the same solution.

This patient has been free from hay-fever practically since Oct. 16, following the third inoculation of vaccine and the second inoculation of ragweed extract. The injection of 2 min. of the ragweed has given rise to such a marked reaction on Oct. 4 and 11 that it was decided to reduce it to  $\frac{1}{4}$  min., and gradually go up till she has taken 6 min. as a final dose with practically no reaction locally. Her general condition has been very markedly improved; has gained in weight and has been feeling well generally. It remains to be seen how she will fare the coming season.

#### SUMMARY AND CONCLUSIONS.

The bacteria found in the secretions of the nose and eyes of hay-fever patients previous to their attacks and during their supposed healthy condition are markedly suggestive of the important rôle played by such bacteria in this disease. The presence of the bacteria and their products is, I believe, the determining factor between individuals being susceptible to hay-fever or not, since they may be, in a measure, responsible for the breaking up of the pollen, setting free the albumens and thus causing pollenosis. The bacterial infection, though secondary to pollenosis, is apparently responsible for the difference between pollenosis, producing a mere transient sneezing, or true hay-fever attacks with all their accompanying symptoms.

The good results obtained by the use of autogenous vaccines, as found in the literature and those I had myself, still further suggest the important relation of bacteria to this disease.

The mechanism underlying pollenosis, with its accompanying anaphylactic symptoms, is still an open question. I have called attention to the recent developments in the physical mechanism of anaphylaxis which can be applied to this disease: The anti-ferments being adsorbed by the liberated pollen albumens, the symptoms are then produced by the free ferments, which are normally present in the system, but unable to produce toxic symptoms because of the action of the anti-ferments. These free ferments produce the anaphylatoxins, and they in turn produce the anaphylactic symptoms of

hay-fever, which resemble so closely anaphylaxis due to other sources.

The underlying reason for the success of the treatment with autogenous vaccine in this disease is, I believe, due to the fact that the infection is due, in practically all the cases, to the staphylococcus group of organisms. (Five of the six cases here reported were due to the staphylococcus, —2 *S.P. aureus* alone, 1 aureus mixed with albus, 1 albus with citreus and 1 albus with strepto. The sixth case showed culturally an unidentified bacillus and a diplococcus resembling the pneumococcus.)

Finally the six cases treated with the autogenous vaccine, here reported, can be said to have resulted in "seasonal cures." The results in these cases have been so decidedly beneficial that one cannot help but conclude that the autogenous vaccine has yielded better results in the treatment of these hay-fever cases than any other therapeutic measure thus far suggested in the treatment of this disease.

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### EMBOLIC PNEUMONIA FOLLOWING THE MASTOID OPERATION; REPORT OF THREE CASES.\*

By GEORGE L. RICHARDS, M.D., FALL RIVER, MASS.

\*Otolologist and Laryngologist, Union Hospital.

DURING the last year I have had three cases showing, after the mastoid operation, symptoms of what has apparently been an embolic infarct of the lung, localized and limited, with the early symptoms of a pneumonia, and with an accompanying pleurisy of the same character. I am wondering if cases such as these are not fairly common, and whether the possible occurrence of localized mural thrombi of the lateral sinus should not be considered in the after-handling of our mastoid cases, even when the classical picture of sinus thrombosis is entirely absent.

\*Read at the Forty-ninth Meeting of the American Otological Society, Washington, D. C., May 10, 1916.

CASE 1. R. W. J. Physician. Acute otitis media in right ear June 14, 1915. Incised under ethyl chloride. Relief. Purulent discharge. June 15th pain; June 16th better; June 17th pain. Incised drum again, ethyl chloride anesthesia. No relief from the pain which continued in spite of free discharge, and on June 20th the x-ray showing involvement of the right mastoid, the usual operation for an acute mastoid was performed. The x-ray findings were confirmed, extensive involvement of all the cells being found. The day following he complained of acute indigestion and nausea. June 21st temperature 100° to 102°; June 22d temperature 101° to 101.2°; June 23d temperature 101.6° to 104°. On this date the high temperature was explained by the appearance of definite erysipelas extending backwards, forwards and upwards from the mastoid area. At this time Dr. George L. Tobey, Jr., of Boston, saw him in consultation, the question of sinus thrombosis being under consideration. As there were no chills, the appearance of the erysipelas served in our minds to explain the temperature, which became normal on June 28th. From June 23d to the 27th there was steady disturbance of the stomach and inability to sleep. Aside from this, convalescence was continuous. On July 1st, by his own insistence, and not by advice, he went home from the hospital. On July 4th, after having felt very well for the preceding two or three days, he had a sudden attack of pain in the right lung just below the nipple, accompanied by a temperature of 101° running up to 102.5°, and the spitting up of some bright blood. A diagnosis was made of a localized pneumonia. On July 14th, the twenty-fifth day of the disease, the temperature became normal. On July 20th there was a similar attack in the opposite lung in about the same relative position, and running clinically almost the same course as to temperature and duration, the latter being about four days. From this time onward convalescence was uneventful. At the time it was first considered, did or did not this patient have a mural thrombus of the lateral sinus, a portion of which on two different occasions was later detached, producing an embolic infarct in each lung with a resultant localized pneumonia?

CASE 2. W. A. came under observation on July 13, 1915, for an acute otitis media. An incision in the drum was made under ethyl chloride anesthesia, resulting in immediate relief, but three days later pain re-occurred and a second incision was made. On July 19th an x-ray picture showed involvement of the left mastoid. He was admitted to the hospital on July 21st and on the 22d an operation for an acute mastoid was performed, the patient taking ether rather poorly. The history in the hospital was uneventful from the 22d to the 29th, the temperature not going above 99.5°, and on the latter date he went home at his own request. Three days later, August 2d, he had a sharp pain in his left side, and the diagnosis of pleurisy was given by the attending physician. I did not see him at his home until several days later. Inasmuch, however, as the pain was sharply localized and the attack of rather short duration, in the light of the other two cases here reported I think he had an embolic pneumonia. Recovery was complete, but it was several weeks before the pain in the side had entirely disappeared.

CASE 3. P. H. Male, fifty years old. Sept. 25, 1915, acute otitis media. Drum incised under ethyl chloride. Sept. 26th x-ray picture showed mastoid

involvement, but he refused operation until Sept. 30th, when the entire mastoid area was found filled with pus and broken-down cells. On the day of admission to the hospital the temperature was 99° and on the next day 101° to 102°. In the early morning of October 2d, he complained of a sharp pain in the left lung very decidedly limited and with all the characteristics of embolic pneumonia. There was bloody sputum for a few hours, then frothy. The rest of the lung on each side was free from trouble. The convalescence was uneventful and he was discharged on Oct. 10th.

#### REMARKS.

In all of these cases there was a sudden attack of pain, which on physical examination appeared to be due to shutting off of a portion of lung, that is, to be the result of an infarct following an embolus and with an accompanying pleurisy. Just such symptoms and just such physical signs might be expected to follow the lodgment of a small mural thrombus from the lateral sinus, and its passage down to the right side of the heart, and thence into the lung. In all three cases the trouble appeared on the side of the operation, and that side only, with the exception of the first case, where both sides were affected,—the side of the operation first. There was no uniformity in the time area, the attacks coming in respectively two days, eleven days, twenty-two and twenty-eight days. In each instance, ethyl chloride had been used as the primary anesthetic. Had this anything to do with the case? I think not.

#### Book Reviews.

*Oral Surgery.* A Treatise on the Diseases, Injuries and Malformations of the Mouth and Associated Parts. By TRUMAN W. BROPHY, M.D., D.D.S., LL.D., Sc.D., F.A.C.S. With special chapters by MATTHEW H. CRYER, M.D., G. HUDSON MAKUEN, M.D., WILLIAM J. YOUNGER, M.D., F. W. BELKNAP, M.D., CALVIN S. CASE, M.D., D.D.S. With 909 illustrations, including 39 plates in colors. Philadelphia: P. Blakiston's Son and Company.

In his preface the author says, "I wish to emphasize an underlying principle of surgery: so to operate as to leave the parts in as nearly a normal anatomical condition as possible; and further, briefly and concisely to supply students, physicians, dentists, and general and oral surgeons with information relative to the symptoms, diagnosis and treatment of conditions affecting the mouth and associated parts."

The author is unable, in spite of efforts to be brief, to give us a book of less than 1100 pages; it is true that a prodigious number of illustra-

tions are included in these pages; many of these pictures are brilliant, and all of them amplify the text. But it seems, from some standpoints, that students would be better served by a shorter text-book.

The volume is very complete; all phases of oral surgery are covered, even to eugenics and infant feeding! The chapter on Tumors is perhaps less proportionately extensive than some of the others; and the entire subject of anesthesia is included in 32 pages of printed matter and illustrations. But, on the whole, the space is divided fairly in relation to the importance of the various subjects.

So large a book upon a special subject is difficult to review adequately. The volume should become an authority, as its author has been for many years.

*Autoplastic Bone Surgery.* By CHARLES DAVISON, M.D., and FRANKLIN D. SMITH, M.D. With 174 illustrations. Philadelphia and New York: Lea and Febiger. 1916.

An admirable and very interesting book of 250 pages. It includes an account of the experimental and clinical work of the authors, and a survey of what seems to them best in the enormous literature which has grown up during the past decade upon this important subject. No final decision is reached in regard to many theoretical considerations, but definite views are offered for practical surgical conditions.

A concise summary at the end of each important chapter is a great convenience to the reader.

The book is cordially recommended to students and surgeons.

*Encyclopedia Medica.* Second edition, under the general editorship of J. W. BALLANTYNE, M.D., C.M., F.R.C.P. Vol. III. Edinburgh and London: W. Green and Son, Ltd. 1916.

The first volume of the new edition of this standard medical encyclopedia was reviewed in the issue of the JOURNAL for Sept. 9, 1915, and the second in the issue for Jan. 27, 1916. This third volume continues the work under the captions from chloroform to dyspnea. The first of these separate articles, and others on cranioleido-dysostosis and on legislation for mental deficiency, are new in this edition. The remaining articles are revised or rewritten. All the articles on drugs have been revised by Dr. John Orr, the author of the section on digitalis. There are few text-cuts in this volume, but several excellent full-page colored plates. The work maintains its important and valuable character.

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## THE ACTION OF ALCOHOL.

ABOUT few scientific questions have there been more dispute and less accurate data than about the physiological action of alcohol. The matter is coming into increasing prominence and the attitude toward it of the medical profession is changing. The extension of the prohibition campaign and the inclusion of social and moral issues have made all the more confusion as to the fundamental facts on which judgment must finally rest.

The recent policy of the New York City Department of Health is significant of the growing opinion that alcohol is a public health problem of first magnitude. The Health Department is not in sympathy with effort to regulate the trade in alcoholic drinks by legislation but believes that a proper education of the people in the actual effect of alcohol is the only logical course, and that this course will eventually bring the proper restriction in the use of alcohol as a beverage. This comes back then to the

question of what is the real action of alcohol.

That alcohol in small doses is burned in the body and spares body and food substance has been proved by Atwater and his associates. Exact and controlled experiments on the physiological action of alcohol on metabolism and the nervous system have, however, been few, and reliable data are correspondingly rare. Benedict outlines a program prepared by the Boston Nutrition Laboratory of the Carnegie Institution for the study of alcohol and describes the results to date. (*Science*, June 30, 1916.) Benedict points out that the use of alcohol as a food beverage, especially in Europe where often the food calories of the alcohol are greater than those from the proteid of the diet, makes it important and within the province of the nutrition laboratory to undertake investigation of the effect of moderate doses. He recognizes the excessive rarity of objectivity as well as of real uncontaminated scientific evidence. Too often the personal ethical views of the observer have dominated the results.

The program outlined by the Nutrition Laboratory provides for thorough study of the physiological effect of alcohol, in small and in repeated doses, on respiration, digestion and secretion, metabolism and heat regulation. Attention is paid to securing careful basic data on the subjects of experiment and in short every effort has been made to forestall criticism even of the ignorant and captious, and to secure and present definite objective data and also to determine a method of procedure which can be followed in future investigations. Particular attention is given to the psychological effects of alcohol.

The selection of the tests to be employed was determined first by the wish to secure a group of systematically coördinated measurements, second to utilize the relatively simple and elementary neuro-muscular phenomena where unknown factors would be reduced to a minimum, and third to select those processes which constituted customary reactions.

Benedict reports that in normal subjects the latent time of the patellar reflex was lengthened on an average by 10%, while the extent of muscle thickening was reduced by 46%. The latent time of the protective lid reflex was increased by 7% and the extent of the lid movement was decreased 19%. The latent time in speech reaction tests was increased 3%. Sensitivity to faradic stimulation was decreased 14%. Little

effect was noted on memory and free association. As for motor coördination, there was a decrease of 9% in the velocity of finger movement and of 11% in the velocity of eye movement. It was observed that the pulse was accelerated, but this Benedict ascribes to inhibition of the inhibitory mechanism of the heart. The greatest changes following the ingestion of alcohol were found to be in those processes least subject to voluntary re-enforcement and control. A considerable practice effect was noted throughout the experiments but even this was more than offset by the action of the alcohol.

The time of the maximum effect of the alcohol was from 90 to 100 minutes after ingestion. Benedict states that contrary to Kraepelin no facilitation effect from alcohol was noted, but that there seemed to be a characteristic depression of the simplest forms of finger and eye movements. He holds this to be presumptive evidence of the effect of alcohol on organic efficiency, but he warns strongly against the uncritical application of these results to industrial processes in general where motor coördination is not the only factor involved.

These studies are not completed and the material already obtained is being further elaborated. Such work when confirmed by independent investigators will give a reliable foundation for the attitude to be assumed toward alcohol as a public health problem.

#### HAY FEVER.

THE present issue of the JOURNAL, which is published as a special number devoted to hay fever and anaphylaxis, contains a series of articles devoted to anaphylactic phenomena especially with reference to the disturbances associated with hay fever. Particular attention is directed to the work of Dr. Goodale and his associates. The author's earlier work upon this subject, which has now a special seasonal interest, was published in the issues of the JOURNAL for November 5, 1914, Vol. clxxi, p. 695, and July 8, 1915, Vol. clxxiii, p. 42. In the former issue there appeared also a preliminary article on asthma in children by Dr. F. B. Talbot, whose latest contribution on this subject is included in the present number.

The importance of hay fever as constituting one of the serious inconveniences—though perhaps not so dangerous—in the lives of many persons is probably underestimated except by those

who are personal sufferers. The number of those affected is perhaps also not fully realized. Careful recent estimates show that there are at least 200,000 persons in the United States who suffer from recurrent annual attacks of the disease. It appears now fairly well determined that hay fever is an anaphylactic manifestation characterized chiefly by vasomotor phenomena.

It is perhaps not generally known that ordinances providing for the cutting of weeds likely to disseminate the disease have been adopted in several American cities. Apparently the first of these was an ordinance, originally passed by the council of the city of Savannah, in August, 1900, providing for the removal of weeds and other rank vegetable growth within the city limits. This law was subsequently amended on July 3, 1910. In substance it provides that the owner of private property, or agents acting in his behalf, shall, upon notice from the health officer of the city of Savannah, cut and remove from such property in the city any weeds or other rank vegetable growth. Penalty for failure to comply with this ordinance is fixed at a fine of \$50.00 or imprisonment for 30 days, or both. Similar ordinances were subsequently passed by New York City and by New Orleans.

#### DIAGNOSTIC CULTURE OF TUBERCLE BACILLUS.

ANY procedure which will facilitate the early diagnosis of pulmonary tuberculosis, especially in the absence of bacilli in the sputum on ordinary examination, is to be welcomed. The method of Petroff for the cultivation of tubercle bacilli is not a radically new procedure, but it offers a practicable means for isolating tubercle bacilli from the sputum as well as from tissues, and often this method of cultivation will show the bacilli when other examinations fail.

The method is roughly as follows: About 5 cc. of sputum under sterile precautions are incubated for half an hour at 37 degrees with 3% sodium hydroxide. After neutralization with hydrochloric acid and centrifugation, the sediment is planted on a special gentian violet egg veal medium, and then incubated at between 38 and 39 degrees. The culture tubes are covered with a mixture of yellow wax and petrolatum to prevent drying.

In describing the application of this method

to the clinical diagnosis of tuberculosis, Keilty (*Jour. Exp. Med.*, July, 1916) concludes that the method is not difficult, requiring only a careful degree of attention to detail. He finds that the method is of very practical value in cases where the bacilli have not been found in ordinary examination of the sputum and that it is a diagnostic procedure which should be employed in such cases. A negative result is of course of no significance. He believes that it supersedes the antiformin method, having all of the good qualities of the latter, and some in addition. It is possible by this method, as Keilty demonstrated, to isolate the tubercle bacillus from a throat swab. He also found that by the digestion of tissue with sodium hydroxide and then cultivation according to Petroff, it was possible to demonstrate the tubercle bacilli in tissue and save time over the slower method of animal inoculation.

#### THE MASSACHUSETTS COMMISSION ON MENTAL DISEASES.

GOVERNOR McCALL has nominated the following as members of the new commission on mental diseases under the terms of Chapter 285 of the Acts of the Legislature of this year, in place of the old State Board of Insanity: Director, George M. Kline, M.D., of Hathorne, with a salary of \$7500, for the term of five years; associate directors, without salary: John B. Tivnan of Salem, for four years; Henry M. Pollock, M.D., of Boston, for three years; Charles G. Dewey, M.D., of Dorchester, for two years; Elmer A. Stevens of Somerville, for one year. We think the Governor has made a wise selection in naming Dr. Kline as director. He is a graduate of University of Michigan Medical Department in 1901, and has established a record as an able administrator while superintendent of the Danvers State Hospital for the Insane during the past four years. He had previously served as assistant physician at the Worcester State Hospital, at the Mt. Pleasant, Iowa, State Hospital, and at the State Psychopathic Hospital of Michigan, where he was for six years before coming to Danvers.

Dr. Pollock is a graduate of the College of Homeopathic Medicine and Surgery of the University of Minnesota in 1897, and is superintendent of the Massachusetts Homeopathic Hospital, having been recently superintendent of the Norwich, Connecticut, Hospital for the Insane. Dr. Dewey is a graduate of Dartmouth

Medical School in 1886, was trained under the late Dr. George F. Jelly, and has been examiner in mental disease in the Institutions Department of the City of Boston for many years. Mr. Tivnan was trustee of the Bridgewater State Farm for fourteen years, and latterly chairman of the board, and he has been identified for a long time with the Plummer Farm School and the Associated Charities of Salem. Mr. Stevens is vice-president of the Massachusetts Trust Company of Boston, and was formerly state treasurer, thus representing the business man on the commission.

Under the law, the director is the administrative and executive head of the commission. He is charged with administering the laws having to do with the classes of persons under the supervision of the commission, of preparing rules and regulations, appointing agents and subordinate officers and fixing their compensation, subject to the approval of the governor and council. The thought comes to the student of medical institutional government that the provision of the law requiring that at least two of the associate board, besides the director, "shall be physicians and experts trained in the care and treatment of the insane"—three out of five directors—is an unnecessary requirement, and hampers the governor in his choice of appointees. The desirable qualities in medical men for such positions are, training in administrative work and the ability to labor harmoniously with others for the good of the service. The new commission is a neutral board and does not represent in its membership the proponents of the outgoing paid board of three commissioners nor the preceding unpaid board with a paid secretary. Whether, as constituted, the associate board will be of great assistance to the director in the transaction of the business of the commission remains to be seen. No doubt the Governor had a difficult task to harmonize the warring elements and to find suitable material. The JOURNAL extends its best wishes to the Commission for a harmonious and efficient career.

#### MEDICAL NOTES.

BUFFALO, N. Y., DEPARTMENT OF HEALTH.—The recently issued report of the Department of Health of Buffalo, N. Y., presents a complete and illuminating account of public health administration in that city. A study of the comparative statistical table points out some im-

portant facts. In 1882, when the city's population was 157,000 there were 4212 deaths with 4800 births, or an excess of only 597 births over deaths; this gave the city a death rate of 24.06 and a birth rate of 27.47 per thousand. In 1915, the population was 461,887, with 6853 deaths and 12,683 births, or an excess of 5830 births over deaths; giving a death rate of 14.83 and a birth rate of 27.45 per thousand. Thus, it will be noted that although the population constantly increased, yet the death rate decreased to such an extent that even the actual number of deaths in 1915 was but 852 in excess of those in 1891, while the population had increased by 6223. On the other hand the difference in births amounted to 4374. An analysis of the ages of death shows that out of a total of 6853, the greatest number (916) died between the ages of 50 and 60 years, and the smallest number (31) between the ages of four and five years. It is also notable that 1630 died under two years of age, and 1935 died between the ages of 60 and 100 years.

**SMALLPOX IN GREECE.**—Report from Athens by way of Paris, on July 20, states that smallpox is at present extensively epidemic in Athens and the Piræus. Compulsory universal vaccination has been ordered. The number of cases is not stated.

**RED CROSS NURSING BUREAU.**—Report from Washington, D. C., on July 31, announces the appointment of Miss Clara D. Noyes, superintendent of the Bellevue Hospital Training School, to be superintendent of the Nursing Bureau of the American Red Cross Society, beginning October 1.

**PROGRESS OF POLIOMYELITIS EPIDEMICS.**—Report from New York on August 4 states that the total number of cases of poliomyelitis in that city during the present epidemic to that date was 4680 with 1025 deaths. In New York State, outside New York City, during the same period there were 545 cases and 51 deaths.

In Massachusetts from July 1 to August 5 there were 131 cases and 17 deaths. Of these, 12 cases were in Boston and 11 each in New Bedford, North Adams, Westfield, and Worcester. In New England, outside of Massachusetts, there have been in Rhode Island 34 cases and six deaths. On Aug. 3 a case was reported at Manchester and one at Keene, N. H.

For the purpose of coordinating research on poliomyelitis, the New York commissioner of health last week invited a number of well known pathologists and bacteriologists throughout the United States to meet in New York City on August 3 and 4, for the purpose of planning a series of investigations likely to effect a successful solution of the problem. Those invited are as follows:

Dr. George J. Adami, McGill University; Dr.

Charles Bass, Tulane University; Dr. Ludwig Hektoen, University of Chicago; Dr. Paul Lewis, Vanderbilt University; Dr. Francis W. Peabody, Peter Bent Brigham Hospital, Boston; Dr. Milton J. Rosenau, Harvard University; Dr. Theobald Smith, Rockefeller Foundation; Dr. Victor Vaughan, University of Michigan and Dr. William H. Welch, Johns Hopkins University.

Associated with these will be the following representatives of the prominent research laboratories in New York City:

Dr. William J. Elser, Dr. Simon Flexner, Dr. Emanuel Libman, Dr. Hideyo Noguchi, Dr. Charles Norris, Dr. William H. Park, Dr. Francis Carter Wood, and Dr. Hans Zinsser.

Those who have already accepted this invitation are Dr. Vaughan, Dr. Rosenau, Dr. Jobling, and Dr. Lewis. The meeting was held in the faculty room of the College of Physicians and Surgeons of Columbia University, and a report of its proceedings will appear in next week's issue of the JOURNAL.

#### EUROPEAN WAR NOTES.

**WAR RELIEF FUNDS.**—On Aug. 5 the totals of the principal New England relief funds for the European War reached the following amounts:

|                              |              |
|------------------------------|--------------|
| Belgian Fund.....            | \$142,153.81 |
| French Wounded Fund.....     | 107,326.51   |
| Armenian Fund.....           | 63,181.73    |
| French Orphanage Fund.....   | 58,741.18    |
| Surgical Dressings Fund..... | 41,893.87    |
| Belgian Tobacco Fund.....    | 33,433.15    |
| Facial Hospital Fund.....    | 23,916.01    |
| Alles' Tobacco Fund.....     | 1,504.75     |

#### MEXICAN NOTES.

**RED CROSS BASE HOSPITALS.**—The full list of twenty-five Red Cross mobile base hospitals under the charge of as skilled surgeons and nurses as our country affords was made public on July 30 by Col. Jefferson R. Kean, Medical Corps, U. S. A., Director General of Military Relief of the American Red Cross. This list not only names the "mother" hospitals and their locations, but in most instances the directors and assistants of the base hospitals, each of which is organized or being organized at an initial cost of \$25,000. Col. Kean also mentions two field columns or ambulance companies. The organizing of these hospitals, which, in war time, would pass under the immediate authority of the War Department and be transported to the base of military operations as they were needed, is considered a piece of war relief preparedness along scientific and constructive lines, and is based in part on the lessons of the European War. The nucleus for the directing personnel of each base hospital is selected from the staff of a large existing civil hospital and when that personnel is transported, on the outbreak of war, to the base of military operations, they

continue at their respective posts, working in the same team-like fashion they employed in civil capacities. Connecting the evacuation or transfer hospitals of the Army with the base hospitals of the Red Cross are the field columns, two of which are being perfected at an expense of about \$15,555 each.

The Director General of Military Relief made this statement concerning the base hospitals and field columns:

"The medical officers attached to regiments, together with those manning the field hospitals and evacuation hospitals, constitute the medical service of the front. These field and evacuation hospitals would, in the opinion of our readers, scarcely deserve the name of hospitals, since they are marching units and have to be provided with only the simplest and most Spartan equipment. Their furniture is bed-sacks, filled with hay and laid on the ground, or camp cots. There are shelter places where the wounded are received, fed, and protected from the weather on their way to the rear. The service of the front is, therefore, the special obligation of the medical officers of the Army and of the National Guard, and the Red Cross is not permitted to share it.

"The next zone, however, which is called the zone of the line of communications and base, is one in which the Red Cross will provide the greater part of service, as the number of medical officers in the Army Medical Corps and connected with the National Guard is quite inadequate to provide such a service. The hospitals provided by the Red Cross, because they are located at the military base, are called base hospitals. They are of great importance, because they are the first real hospitals provided with beds, mattresses, sheets, and trained nurses which the wounded soldier finds on his journey to the rear.

"The base hospitals will receive regular, volunteer, and national guardsman alike, and so every soldier whose duty brings him within range of hostile bullets has reason to take a keen, personal interest in the knowledge that in these hospitals is being now enrolled the most distinguished talent in the medical profession in this country.

"Each division of troops requires at least one base hospital. It is equipped to receive 500 patients. Its professional staff consists of 23 physicians and surgeons, two dental surgeons, a chaplain, and 50 trained nurses. To assist the latter are enrolled 25 volunteer nurses' aids. The enlisted personnel numbers 153, while authority is given for the employment of about 15 civilians.

"The Naval base hospitals, of which several are now in course of organization, are of about one-half the size of the Army hospitals. The medical equipment of one of the Army base hospitals is estimated to cost about \$25,000, and of a Naval base hospital about \$15,000.

"This equipment should be purchased in time of peace and kept in store by the government, as, if properly stored, very few of the articles suffer much deterioration, and if the purchase is put off until time of war it is only with great delay and difficulty that it can be secured. To avoid this delay and to render the units promptly fit for service many of the Red Cross Chapters in cities where base hospital units are being organized have raised money to purchase it.

"It was anticipated that arrangements could easily be made for the storage of this equipment service on government reservations, but in this expectation the Red Cross has been disappointed, and most of the Chapters now find that they must make further appeal to individual patriotism and generosity to obtain a storage place for it.

"The great advantage of organizing these units in connection with large civil hospitals is that in this way is secured a personnel who know each other and who are accustomed to work together so that team-work and good organization are possible at the outset."

The following are the Red Cross base hospitals already organized:

*Presbyterian Hospital*, New York City—(Equipment subscribed): Director, Dr. George E. Brewer, also Chief of Surgical Service; Principal Assistant, Dr. Alfred Stillman; Chief of Medical Service, Dr. Warfield T. Longcope; Chief of Laboratory Service, Dr. Karl M. Vogel; Chief Nurse, Miss Anna C. Maxwell.

*Mount Sinai Hospital*, New York City—(Equipment subscribed): Director, Dr. N. E. Brill; Chief of Surgical Service, Dr. Howard Lilienthal; Chief of Medical Service, Dr. R. Weil; Chief of Laboratory Service, Dr. George Baehr; Chief Nurse, Miss Elizabeth A. Greener.

*Bellevue Hospital*, New York City—(Equipment subscribed): Director, Dr. George David Stewart, also Chief of Surgical Service; Chief of Medical Service, Dr. Van Horne Norris; Chief of Laboratory Service, Dr. Charles Norris; Chief Nurse, Miss Clara D. Noyes.

*New York Hospital*, New York City—(Equipment subscribed): Director, Dr. Charles L. Gibson, also Chief of Surgical Service; Chief of Medical Service, Dr. Lewis A. Conner, Chief of Laboratory Service, Dr. William J. Elser; Chief Nurse, Miss M. H. Jordan.

*New York Post Graduate Hospital*, New York City—(Equipment subscribed): Director, Dr. Samuel Lloyd; Chief of Surgical Service, Dr. Edward W. Peterson; Chief of Medical Service, Dr. Arthur F. Chace; Chief of Laboratory Service, Dr. Ward J. MacNeal; Chief Nurse, Miss Amy Patmore.

*Brooklyn, N. Y., for Navy*—Equipment subscribed: Director, Dr. W. B. Brinsmade, also Chief of Surgical Service; Chief of Medical Service, Dr. Luther F. Warren; Chief of Laboratory Service, Dr. Robert F. Barber; Chief Nurse, Miss Frances Van Ingen; Asst., Mrs. Lillian H. Read.

*Massachusetts General Hospital, Boston, Mass.*—(Equipment subscribed): Director, Dr. Frederic A. Washburn; Chief of Surgical Service, Dr. George W. W. Brewster; Chief of Medical Service, Dr. Richard C. Cabot; Chief of Laboratory Service, Dr. J. Homer Wright; Chief Nurse, Miss Sara E. Parsons.

*Boston City Hospital, Boston, Mass.*—(Equipment subscribed): Director, Dr. J. J. Dowling; Chief of Surgical Service, Dr. Edward H. Nichols; Chief of Medical Service, Dr. John Jenks Thomas; Chief of Laboratory Service, Dr. Ariel W. George; Chief Nurse, Miss Emma M. Nichols.

*Harvard University, Cambridge, Mass.*—(Equipment subscribed): Director, Dr. Harvey Cushing, also Chief of Surgical Service; Chief of Medical Service, Dr. Roger I. Lee; Chief of Laboratory Service, Dr. Richard P. Strong; Chief Nurse, Miss Carrie M. Hall.

*Lakeside Hospital, Cleveland, O.*—(Equipment subscribed): Director, Dr. George W. Crile; Chief of Surgical Service, Dr. W. E. Lower; Chief of Medical Service, Dr. C. F. Hoover; Chief of Laboratory Service, Dr. H. T. Karsner; Chief Nurse, Miss Grace Allison.

*Rochester, N. Y.*—Director, Dr. John M. Swan; Chief of Surgical Service, Dr. C. W. Hennington; Chief of Medical Service, Dr. William V. Ewers; Chief of Laboratory Service, Dr. C. C. Sutter; Chief Nurse, Miss Emma Jones; Asst., Miss Jessica Heal.

*Johns Hopkins Hospital, Baltimore, Md.*—Director, Dr. Winford Smith; Chief of Surgical Service, Dr. J. M. T. Finney; Chief of Medical Service, Dr. T. C. Janeway; Chief of Laboratory Service, Dr. T. R. Boggs; Chief Nurse, Miss Bessie E. Baker.

*Harper Hospital, Detroit, Mich.*—Director, Dr. Angus McLean; Chief of Surgical Service, Dr. C. D. Brooks; Chief of Medical Service, Dr. B. R. Shurley; Chief of Laboratory Service, Dr. P. M. Hickey; Chief Nurse, Miss Emily McLaughlin.

*University of Pennsylvania, Philadelphia, Pa.*—Director, Dr. Edward Martin; Chief of Surgical Service, Dr. John Deaver; Chief of Medical Service, Dr. Alfred Stengel; Chief of Lab-

oratory Service, Dr. Alan J. Smith; Chief Nurse, Miss Irwin.

*Pennsylvania Hospital, Philadelphia, Pa.*—(Equipment subscribed): Director, Dr. Fred H. Harte; Chief of Surgical Service, Dr. John H. Gibbon; Chief of Medical Service, Dr. George W. Norris; Chief of Laboratory Service, Dr. Edward Krumbhaar; Chief Nurse, Miss Elizabeth Dunlop.

*Barnes Hospital, Washington University, St. Louis, Mo.*—(In process of organization): Director, Dr. Fred T. Murphy; Chief of Surgical Service, Dr. Malvern Clouston; Chief of Medical Service, Dr. Walter Fisehell; Chief of Laboratory Service, Dr. Eugene L. Opie; Chief Nurse, Miss Julia Stimson.

*Chicago, St. Joseph, St. Mary and Augustana Hospitals.*—(Equipment subscribed): Director, Dr. Albert J. Ochsner, also Chief of Surgical Service; Chief of Laboratory Service, Dr. Oscar Nadean; Chief Nurse, Mrs. Julie Flekke.

*Chicago, Mercy and Wesley Hospitals.*—(Equipment Subscribed): Director, Dr. Fred A. Besley; Chief of Surgical Service, Dr. Joseph Jaros; Chief of Medical Service, Dr. Milton Mandell; Chief Nurse, Miss Daisy Ureh.

*Cincinnati, O.*—Director, Dr. G. A. L. Reed.  
*University of Pittsburgh, Pittsburgh, Pa.*—Director, Dr. R. T. Miller.

*Chicago, Presbyterian and County Hospitals.*—(Equipment subscribed): Director, Dr. Frank Billings; Chief of Surgical Service, Dr. Arthur Dean Bevan; Chief of Medical Service, Dr. Ernest E. Irons; Chief of Laboratory Service, Dr. Homer K. Nicoll; Chief Nurse, Miss Mabel K. Adams.

*Chicago, St. Luke's and Michael Reese Hospitals.*—(Equipment subscribed): Director, Dr. L. L. McArthur.

*Lincoln Hospital, N. Y.*—(Equipment subscribed): Director, Dr. Frank Gwyer.

*Rochester, Minn., The Mayo Clinic.*—Director, Dr. Edward S. Judd.

*The German Hospital, New York City.*—Director, Dr. Frederick Kammerer.

#### FIELD COLUMNS.

(Ambulance Companies)

*New York City.*—(\$10,000 subscribed for equipment); Director, Dr. T. M. Strong.

*Berkeley, Calif.*—Director, Dr. R. T. Legge.

MEXICAN RELIEF FUNDS.—On Aug. 5 the totals of the principal funds for the relief of Massachusetts troops on the Mexican frontier reached the following amounts:—

|                           |             |
|---------------------------|-------------|
| Volunteer Aid Fund.....   | \$74,467.65 |
| Home Relief Fund.....     | 2,508.00    |
| Eighth Regiment Fund..... | 2,225.00    |

#### BOSTON AND NEW ENGLAND.

DIPHTHERIA AT MASSACHUSETTS GENERAL HOSPITAL.—An outbreak of diphtheria has recently occurred at the Massachusetts General Hospital. On Aug. 6 there were 32 positive cases of the disease, including 29 nurses, two physicians, and one ambulance driver. No patients have been infected and there have been no fatalities. The source of the outbreak is as yet undetermined.

HAVERHILL BOARD OF HEALTH.—The thirty-sixth annual report of the Haverhill, Mass., Board of Health states that the death rate of that city for the year 1915 was 13.75 per thousand inhabitants, this being the lowest mortality rate in the history of the city. The total number of deaths was 677. The average age of decedents during the year was 45 years, 10 months and 14 days, the highest in the past thirty-five years.

MASSACHUSETTS BOARDS OF HEALTH.—A quarterly meeting of the Massachusetts Association of Boards of Health was held on July 27 at Providence City Hospital with about 75 members in attendance. Addresses were made by Mayor Gayner of Providence, Dr. Charles V. Chapin, Superintendent of Health of Providence, and by Mr. Franz Schneider, Jr., of the Russell Sage Foundation of New York City, on Relative Values in Public Health Work.

ANTHRAX IN MASSACHUSETTS.—The Massachusetts Board of Labor and Industries has recently conducted a statistical study of anthrax in this commonwealth. During the year 1915, there were 30 human cases of this disease in Massachusetts, with six deaths. During the year 1916 thus far there have been 22 cases and five deaths.

#### Miscellany.

##### CHANGES IN THE MEDICAL CORPS, U. S. NAVY, FOR THE WEEK ENDING JULY 22, 1916.

July 11.

Surgeon C. D. Langhorne, detached *Oklahoma* to two months leave.

Surgeon M. K. Johnson, detached *Montana* to *Oklahoma*.

July 12.

P. A. Surgeon C. P. Lynch, commissioned from February 19, 1916.

Asst. Surgeon O. C. Foote, detached *Tallahassee* to *Delaware*.

July 13.

Asst. Surgeon Howard Priest, detached *Delaware* to *Tallahassee*.

Asst. Surgeon R. H. Greenough, commissioned May 25, 1916.

July 17.

Asst. Surgeon J. T. Boone, detached Marine Brigade, Haiti, to treatment, Naval Hospital, Norfolk, Va.

Asst. Surgeon C. F. Glenn, M.R.C., to Naval Recruiting Station, Burlington, Vt.

Asst. Surgeon G. E. Faulkner, M.R.C., to Recruiting Station, Naval, New Orleans, La.

Asst. Surgeon L. D. Arbuckle, M.R.C., to Navy Recruiting Station, Boston, Mass.

July 18.

P. A. Surgeon J. A. Biello, temporary duty, Naval Recruiting Station, New York, N. Y.

July 19.

Asst. Surgeon Henry McDonald, detached *Colorado* to *Pittsburgh*.

#### APPOINTMENTS.

Dr. Victor V. Anderson has been appointed to take charge of the Medical Department and Psychological Laboratory of the Boston Police Corps.

Dr. Lyman A. Jones, formerly district health officer in Berkshire and later in Essex, Mass., has been appointed to succeed Prof. Selskar M. Gunn as director of hygiene of the Massachusetts State Department of Health.

#### RECENT DEATHS.

DR. GEORGE ARTHUR STONE died at his home in Pigeon Cove, Rockport, Mass., July 28, aged 50 years. Dr. Stone was born in Ipswich, Mass., was a graduate of Harvard Medical School in 1889, and joined the Massachusetts Medical Society in the same year. He had practised in Pigeon Cove for 18 years and had been a member of the school board. He was a Mason. He is survived by a widow and one son.

DR. MICHAEL KELLY, a pediatricist of Fall River, Mass., died in that city July 28, aged 62 years. He was born in Ireland, went to Fall River in 1869 and graduated from Holy Cross College in 1879, and from Bellevue Medical College in 1885 when he settled in practice in Fall River. He was chairman of the board of health for seven years, and was a member of the Massachusetts Medical Society from 1901 until February of this year. He leaves a wife and three children.

DR. ADOLPH LAMAR who died of heart disease on July 25, in New York City, was born at Havana, Cuba, in 1869. He was a graduate of the University of Havana and a practitioner and member of the board of health in that city. He is survived by his widow and one daughter.

DR. L. ALBERT NEISSER, Professor of Dermatology in the University of Breslau, died at Berlin on July 30.

DR. SAMUEL SILVA, who died of cerebral hemorrhage on July 30 at Southbridge, Mass., was born at Fayal in the Azores, in 1836. He was a graduate of the Harvard Dental School and had practised his profession in Southbridge for many years.